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CONTENTS OF PREVIOUS NUMBER

AUGUST, 1932. NUMBER 2

Pericarditis. Harry L. Smith, M.D., and Fredrick A. Willius, M.D., Rochester, Minn.
I. Chronic Adherent Pericarditis.
II. Calcification of Pericardium.
III. Pericarditis with Effusion.

Cholesterol of the Blood Plasma in Hepatic and Biliary Diseases. Emanuel Z. Epstein, M.D., New York.

Anemia Associated with Biliary Fistula. S. V. Balderston, M.D., Evanston, Ill.

Carbohydrate Metabolism in a Case of Hemochromatosis. Richard P. Stetson, M.D., and John P. Peters, M.D., New Haven, Conn.

Hemochromatosis and Purpura. Richard P. Stetson, M.D., and Henry W. Ferris, M.D., New Haven, Conn.

Importance of Hepatomegaly and Splenomegaly in Differential Diagnosis. Moses Barron, M.D., and A. B. Litman, M.D., Minneapolis.

Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes: III. Chloroform Poisoning. T. L. Althausen, M.D., San Francisco, and E. Thoenes, Dr.med., Leipzig, Germany.

Treatment of Lobar Pneumonia with Carbon Dioxide and Oxygen: Report of Twenty-Seven Cases. J. Fletcher Hanson, M.D., and Abner W. Calhoun, M.D., Atlanta, Ga.

Quinine Derivatives and Specific Immune Serum in the Treatment of Pneumococcus Infection. Hobart A. Reimann, M.D., and Johannes K. Moen, M.D., Minneapolis.

Resuscitation of the Stopped Heart by Intracardial Therapy: II. Experimental Use of an Artificial Pacemaker. Albert S. Hyman, M.D., New York.

Fibromyoma of the Uterus, Cardiac Failure, Anemia and Edema: Report of a Case. H. Brandman, M.D., Chicago.

Hyperparathyroidism Without Parathyroid Tumor: Report of a Case Improved by Partial Parathyroidectomy. Lewis H. Hitzrot, M.D., and Bernard I. Comroe, M.D., Philadelphia.

Relations Between Primary Hypochromic Anemia and Chlorosis. Arthur L. Bloomfield, M.D., San Francisco.

Relation of Pain of Peptic Ulcer to Gastric Motility and Acidity. Jacob Meyer, M.D.; Dorothy Fetter, Ph.D., and Alfred A. Strauss, M.D., Chicago.

Book Reviews.

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Archives of Internal Medicine

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UREA CLEARANCE TEST AS AN INDEX OF RENAL FUNCTION

I. STUDIES OF NORMAL SUBJECTS

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In 1921, Austin, Stillman and Van Slyke,[1] while developing the urea secretory constant, discovered two laws of urea excretion. They found that the normal rate of urea excretion in man and dog increases, first, in direct proportion to the blood urea concentration, and second, in proportion to the square root of the urinary volume per unit of body weight. They also showed that a rising volume of urine is not indefinitely accompanied by an increase in the output of urea. The point at which an acceleration of the urinary flow is not paralleled by further elimination of urea they termed the "augmentation limit," and placed it between 2.5 and 6 liters of urine per twenty-four hours in normal persons, that is, from 1.7 to 4.1 cc. per minute.

These original concepts were verified in 1928 by Möller, McIntosh and Van Slyke,[2] who in a study of seven normal persons found that the "augmentation limit" was between 1.67 and 2.55 cc. of urine output per minute. The amount of blood cleared of urea in one minute under these conditions of urinary activity they termed the maximum urea clearance (C_m). They found this to average about 75 cc. of blood in normal persons. In other words, efficient kidneys excreting urine at any rate above 2 cc. per minute can clear about 75 cc. of blood of its urea in one minute. This figure can be calculated from the urea concentrations in the blood and urine (B and U, respectively) and the urine output in cubic centimeters per minute (V) as follows:

$$\text{Maximum clearance } (C_m) = \frac{UV}{B}$$

For volumes of urine of less than 2 cc. per minute, Möller, McIntosh and Van Slyke [2] calculated the standard clearance (C_s), which repre-

From the Harriet Weil Memorial Fund, Department of Medicine, New York Post-Graduate Medical School and Hospital.

* Oliver Rea Fellow in Medicine.

1. Austin, J. H.; Stillman, E., and Van Slyke, D. D.: Factors Governing the Excretion Rate of Urea, J. Biol. Chem. **46**:91, 1921.

2. Möller, E.; McIntosh, J. F., and Van Slyke, D. D.: Studies of Urea Excretion: II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, J. Clin. Investigation **6**:427, 1928.

sents the amount of blood cleared of its urea when the urine volume is at the average level of 1 cc. per minute. They found this to average about 54 cc. of blood; that is, normal kidneys excreting urine at the average rate of 1 cc. per minute can clear about 54 cc. of blood of its urea in one minute. This figure can be calculated as follows, U, B and V denoting the same elements as in the foregoing equation:

$$\text{Standard clearance } (C_s) = \frac{U\sqrt{V}}{B}$$

Taylor, Drury and Addis [3] have shown that the urea excretion ratio of Addis,[4] which is analogous to the maximum urea clearance, varies with the surface area of the body more than it does with the weight. In a second paper, McIntosh, Möller and Van Slyke [5] verified this for the urea clearance, and found that more constant normal values can be obtained if the volume of urine excreted by the subject is corrected for surface area. In a recent paper, Ralli, Brown and Pariente [6] have shown that the determination of the standard clearance in normal dogs gives more uniform results if the amount of blood cleared of its urea is determined for a unit of surface area of the body. Basing their calculations on medico-actuarial tables, Van Slyke [5] and his co-workers have adopted 1.73 square meters as the average surface area. The corrected volume of urine output is determined as follows:

$$V_c = V \times \frac{1.73}{S.A.}$$

V equals the observed excretion of urine per minute in cubic centimeters and $S.A.$ equals the surface area of the body.

The present report is based on a study of the urea clearance in normal human subjects. All collections of urine and blood were made by one of us personally. The persons investigated were studied for at least two successive hours on the same day, and the average clearance was determined. In all cases the urine volumes were corrected for surface area.

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3. Taylor, F. B.; Drury, D. R., and Addis, T.: The Regulation of Renal Activity: VIII. The Relation Between the Rate of Urea Excretion and the Size of the Kidneys, Am. J. Physiol. **65**:55, 1923.

4. Addis, T., and Watanabe, C. K.: A Method for the Measurement of the Urea Excreting Function of the Kidney, J. Biol. Chem. **28**:251, 1916. Addis, T.: Renal Function and the Amount of Functioning Tissue, Arch. Int. Med. **30**:378 (Sept.) 1922.

5. McIntosh, J. F.; Möller, E., and Van Slyke, D. D.: Studies of Urea Excretion: III. The Influence of Body Size on Urea Output, J. Clin. Investigation **6**:467, 1928.

6. Ralli, E. P.; Brown, M., and Pariente, A.: The Urea Clearance Test in Normal Dogs, Am. J. Physiol. **97**:432, 1931.

PROCEDURE

The procedure suggested by Möller, McIntosh and Van Slyke [2] was used throughout these studies. Breakfast was allowed but coffee was withheld, since Addis and Drury [7] have shown that coffee increases the urea clearance. The subjects, however, were not put to bed, but performed their usual laboratory, clerical or hospital duties. This was done because we wished to investigate the effect of moderate exercise on the blood urea clearance and thus determine the possibility of applying the urea clearance test to patients seen and studied in a physician's office or a hospital dispensary.

The test was carried out as follows (all steps were timed to the fraction of a minute).

9.00 a. m.: Bladder emptied; urine discarded.

10.00 a. m.: Bladder emptied; urine volume measured; urea nitrogen determined.

10.05 a. m.: Sample of blood obtained by venous puncture; urea nitrogen determined.

11.00 a. m.: Bladder emptied; urine volume measured; urea nitrogen determined.

The height and weight were then determined.

In some instances the urea clearance was studied for four consecutive hours; when the test was thus prolonged another specimen of blood was obtained two hours after the first, and the urea content of this second blood sample was used to calculate the clearances for the last two hours.

In every case the procedure was carried out in the morning, since MacKay [8] has shown that urea excretion is least liable to marked fluctuation in the morning hours.

The urea nitrogen in the blood and in the urine was determined by the gasometric urease method of Van Slyke.[9]

Urine volumes were always corrected for surface area, DuBois tables being used. The standard adopted for body area was 1.73 square meters. For urine rates less than 2 cc. per minute, the standard clearance was determined by the following formula:

$$C_s = \frac{U\sqrt{V_c}}{B}$$

U equals the urine urea nitrogen in milligrams per hundred cubic centimeters. B equals the blood urea nitrogen in milligrams per hundred cubic centimeters and V_c equals the amount of urine (in cubic centimeters) per minute $\times \frac{1.73}{\text{surface area of subject.}}$

For rates of urine flow above 2 cc. per minute, the maximum clearance was determined according to the formula:

$$C_m = \frac{UV_c}{B}$$

U, B and V_c denote the same elements as in the foregoing equation.

7. Addis, T., and Drury, D. R.: The Rate of Urea Excretion: VII. The Effect of Various Other Factors than Blood Urea Concentration on the Rate of Urea Excretion, J. Biol. Chem. **55**:629, 1923.

8. MacKay, E. M.: Studies of Urea Excretion: V. The Diurnal Variation of Urea Excretion in Normal Individuals and Patients with Bright's Disease, J. Clin. Investigation **6**:505, 1928.

9. Van Slyke, D. D.: Determination of Urea by Gasometric Measurement of Carbon Dioxide Formed by the Action of Urease, J. Biol. Chem. **73**:695, 1927.

TABLE 1.—*Urea Clearance Tests in Normal Subjects*

Subject	Time, A.M.	*V* Urine Volume, Cc. per Min.	*Vc* Urine Volume Corrected for Surface Area, Cc. per Min.	*U* Urine Urea Nitrogen, Mg. per 100 Cc.	*B* Blood Urea Nitrogen, Mg. per 100 Cc.	Maximum Clearance Calculated for Urine Volumes Above, 2 Cc. per Min.	Standard Clearance Calculated for Urine Volumes Below, 2 Cc. per Min.	Percentage of Normal Value Calculated on Basis of $C_s = 54$ $C_m = 75$
1. M. B.	9-10	1.28	1.20	741.8	12.66	....	64.4	119.1
	10-11	1.01	0.95	899.2	.....	....	70.2	129.8
2. B. I. A.	10-11	0.82	0.79	977.0	12.04	....	71.4	132.2
	11-12	0.70	0.68	983.0	.....	....	67.0	123.9
3. H. D.	10-11	0.48	0.53	990.2	12.82	....	56.4	104.3
	11-12	0.48	0.53	1108.3	.....	....	62.2	115.1
4. M. B.	10-11	0.86	0.79	1075.1	13.31	....	71.9	133.0
	11-12	0.95	0.87	922.4	.....	....	64.4	119.2
	12- 1	1.09	1.00	842.4	12.91	....	64.6	119.5
	1- 2	0.95	0.87	833.3	.....	....	60.0	111.1
5. H. J. J.	9-10	0.91	0.73	1155.0	12.71	....	77.7	143.8
	10-11	0.85	0.68	995.7	.....	....	64.6	119.4
	11-12	0.56	0.45	1241.1	12.39	....	67.1	124.2
	12- 1	0.64	0.52	1199.8	.....	....	69.5	128.7
6. W. V. S.	9-10	0.57	0.53	1067.1	12.14	....	63.7	117.9
	10-11	0.90	0.83	780.9	.....	....	58.4	108.1
	11-12	0.78	0.72	812.9	12.97	....	53.0	98.1
	12- 1	0.86	0.79	757.8	.....	....	51.8	95.9
7. A. J. M.	9-10	1.05	0.93	1009.5	13.59	....	71.6	132.4
	10-11	1.04	0.92	760.7	.....	....	53.5	99.3
	11-12	2.61	2.29	325.6	.....	54.8	....	73.0
	12- 1	1.07	0.94	590.5	.....	....	42.3	78.2
8. R. A. D.	9-10	0.19	0.19	1669.6	9.91	....	73.1	135.3
	10-11	0.36	0.36	1547.4	.....	....	93.7	173.3
	11-12	0.49	0.48	1299.5	9.38	....	89.7	165.9
	12- 1	0.58	0.58	873.9	.....	....	70.8	130.9
9. T. S.	10-11	0.38	0.44	1149.4	9.64	....	78.7	145.5
	11-12	0.48	0.55	1003.9	.....	....	77.1	142.6
10. H. D.	10-11	0.73	0.81	730.6	5.95	....	110.5	204.4
	11-12	0.54	0.60	772.8	.....	....	100.0	185.0

TABLE 2.—*Summary of Urea Clearance in Normal Subjects*

Subject	Number of Observations	Standard Clearance			Percentage of Normal Value Calculated on Basis of $C_s = 54$ $C_m = 75$		
		Average	Maximum	Minimum	Average	Maximum	Minimum
M. B.	6	65.9	71.9	60.0	121.9	133.0	111.1
H. J. J.	4	69.7	77.7	64.5	129.0	143.8	119.4
R. A. D.	4	81.8	93.7	70.8	151.3	173.3	130.9
W. V. S.	4	56.7	63.7	51.8	105.0	117.9	95.9
A. J. M.	4	55.5	71.5	42.3	95.7	132.4	73.0
H. D.	4	82.2	110.5	56.4	152.2	204.4	104.3
B. I. A.	2	69.2	71.4	67.0	128.1	132.2	123.9
T. S.	2	77.9	78.7	77.0	144.0	145.5	142.6

Total Standard Clearance (Thirty Hours on Eight Normal Subjects)

Mean	69.6
Maximum	82.2
Minimum	55.5
Maximum observed deviation of an individual mean from mean of group =	±13

RESULTS

Thirty hours of observation was carried out on eight normal subjects. The results are given in tables 1 and 2. The average standard clearances varied from 55.5 to 82.2 cc. of blood. The mean for the whole group was 69.6 cc. In a study of their own normal values and those calculated from data in the literature, a total of one hundred and eight hours of observation on eighteen normal subjects, Möller, McIntosh and Van Slyke [2] noted variations in the standard clearances of from 40.1 to 68.3 cc. of blood with a mean of 54.5 cc.

Addis and Drury [7] and Mackay [8] have shown that strenuous and prolonged exercise, such as running for one hour or playing several sets of tennis, diminishes the blood urea clearance. MacKay assumed that hard exercise probably increases the blood flow to muscular tissues, resulting in a diminution in the renal circulation. In our studies, however, the subjects carried out their routine duties which did not entail severe exertion. The average amount of blood cleared of urea per unit of time in our cases was distinctly higher than that recorded by Möller, McIntosh and Van Slyke,[2] who kept their subjects in bed. The maximum deviation from the mean of the group in both series, however, was the same, namely ± 13 cc. We can assume, therefore, that the very moderate exercise allowed our subjects raised the blood urea clearance, possibly owing to an increased renal circulation.

At first we believed that this finding would require an alteration of the normal standard in the calculation of renal function as a percentage of the normal value for cases of Bright's disease seen and studied in a hospital dispensary or in a physician's office, since such patients make a certain amount of physical effort to reach the physician. It soon became apparent, however, as will be seen later, that when renal impairment exists, the kidney is far from labile, and moderate exercise is without influence on the blood urea clearance.

COMMENT

In this and in subsequent papers, we have expressed the urea clearance as a percentage of the normal value, using Van Slyke's figures of 54 cc. of blood for the normal average standard clearance and 75 cc. for the normal average maximum clearance. That is, if a person has a standard clearance of 54 cc. of blood, he is considered to have 100 per cent of urea clearance. If he has a standard clearance of 27 cc. of blood, his urea clearance is only 50 per cent of normal and so on. The percentage of normal clearance can readily be obtained by multiplying the standard and maximum clearances by the factors 1.85 and 1.33, respectively.

A study of the protocols of Van Slyke and his collaborators and of our own makes it apparent that the percentage of urea clearance varies markedly in a normal person. Within three hours a subject may show a variation of from 132 to 73 per cent in the urea clearance (A.J.M., 7, table 1). In the same subject, studied on different days, the urea clearance may vary between 204 and 104 per cent (H.D., 3 and 10, table 1). On the whole, the variations recorded by us are no greater than those observed by Van Slyke and his associates.

It may be mentioned here that as the urea clearance diminishes, with impaired renal function, it shows fewer variations and becomes more and more fixed, resembling in this respect the specific gravity of the urine. The normal kidney, however, is extremely labile; its functional elasticity is indicative of its normality. Unlike the diseased organ, the normal kidney responds by increased or decreased activity to moderate exercise, to severe exertion, to drugs, to various kinds of food and in all probability to many other factors.

We cannot conceive that the urea clearance could be fixed in normal persons irrespective of any attempts to standardize the conditions of the test. The glomeruli in the normal kidney, as Wearn and Richards [10] have shown, function intermittently, and according to the prevailing diuretic stimuli only a few or a great many may be active; there may be a large amount of blood flowing through the glomeruli or none at all; the intraglomerular blood pressure varies a great deal; the nerve fibers that exist between the tubules and in the glomerular tuft indicate a nervous control of renal activity. For these reasons and many others, it may be safely concluded that the normal kidney has enormous reserve power and varies its pace accordingly. We stress this point because the figure 100 per cent, or any other per cent, of urea clearance is relative to many controlled and uncontrolled, and many known and unknown, factors, at least in normal subjects. The absolute value of the kidney function of any normal person is not determined by the present test or by any other. Of far greater significance as a measure of renal efficiency is the degree of variation in the functional capacity of the kidney, which reflects renal effort and reserve. The urea clearance, like the specific gravity of the urine, when studied in normal subjects bears out this point well.

We shall have occasion to show that the figures for urea clearance are of clinical value, but they should not be interpreted dogmatically as absolute values of renal function. Fifty per cent of average normal urea clearance does not have the same relative significance, nor does it

10. Wearn, J. F., and Richards, A. N.: Observations on the Composition of Glomerular Urine with Particular Reference to the Problem of Reabsorption in the Renal Tubules, Am. J. Physiol. **71**:209, 1924.

merit the same evaluation as, for instance, a hemoglobin reading. Normal subjects are known to have given values of 52 per cent (Van Slyke) and 58 per cent [11] on single observations. Of far greater importance are clearance values repeatedly and consistently low, reflecting fixation of renal effort, which is characteristic of kidney impairment.

SUMMARY

Thirty hours of clearance studies in eight normal subjects under moderate exertion are reported. A comparison of our data with those published by Möller, McIntosh and Van Slyke [2] shows that moderate exercise definitely increases the blood urea clearance of normal persons, compared to that of persons lying down throughout the test.

The blood urea clearance varies a great deal in normal persons. A fixation of the clearance values at a low level is necessary to establish the existence of an impairment of kidney function. A single determination as low as 52 per cent of normal is not necessarily an indication of diminished renal activity.

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11. Bruger, M., and Mosenthal, Herman O.: Urea Clearance Test as an Index of Renal Function: II. The Effect of Ingestion of Carbohydrate (Dextrose), Arch. Int. Med., this issue, p. 358.

UREA CLEARANCE TEST AS AN INDEX OF RENAL FUNCTION

II. THE EFFECT OF INGESTION OF CARBOHYDRATE (DEXTROSE)

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The influence on the blood urea clearance of the ingestion of carbohydrate in the form of dextrose was studied in six persons. The subjects were normal, except that they were reported to have exhibited glycosuria at some previous time. The sugar tolerance test showed that, in regard to their carbohydrate metabolism, three of the subjects were normal, two showed a diminished tolerance for carbohydrates and one had renal glycosuria. None of these disturbances should influence the function of the kidney, as far as the elimination of urea is concerned. By timing carefully the taking of the specimens of urine and blood, we were able to study the blood urea clearance over shorter and longer periods before and after the ingestion of 100 Gm. of dextrose (table 1).

PROCEDURE

The urea clearance tests were carried out in the same fashion as those described in the preceding paper of this series,[1] except that the time intervals were varied somewhat, and that 100 Gm. of dextrose was administered after the first timed specimen of urine had been obtained. The details of these variations are made clear in table 1.

The subjects investigated were not kept in bed but, except for maintaining the sitting posture, were at complete rest in the intervals between the taking of the specimens of blood and of urine. The conditions, therefore, approached more closely those of Möller, McIntosh and Van Slyke [2] than those described in the preceding paper.

RESULTS

Twenty-eight observations were carried out on six subjects. The results are given in tables 1 and 2. The average standard clearances

From the Harriet Weil Memorial Fund, Department of Medicine, New York Post-Graduate Medical School and Hospital.

* Oliver Rea Fellow in Medicine.

1. Bruger, M., and Mosenthal, H. O.: Urea Clearance Test as an Index of Renal Function: I. Studies of Normal Subjects, Arch. Int. Med., this issue, p. 351.

2. Möller, E.; McIntosh, E. F., and Van Slyke, D. D.: Studies of Urea Excretion: II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, J. Clin. Investigation **6**:427, 1928.

TABLE 1.—*Effect of Ingestion of Dextrose on the Urea Clearance*

Subject	Time of Collection of Urine	V Urine Volume, Cc. per Minute	Vc Urine Volume Corrected for Surface Area, Cc. per Minute	U Urine Urea Nitrogen, Mg. per 100 Cc.	B Blood Urea Nitrogen, Mg. per 100 Cc.	Maximum Clearance Calculated for Urine Volumes Above 2 Cc. per Minute	Standard Clearance Calculated for Urine Volumes Below 2 Cc. per Minute	Percentage of Normal Calculated on Basis of Cs = 54 Cm = 75	Comment
1	7:55 – 9:24½	1.16	0.90	831.0	9.67	....	81.6	150.9	100 Gm. dextrose
J. M. H.	9:24½– 9:48	0.72	0.56	783.6	10.03	....	58.5	108.3	at 9:25
	9:48 –10:08½	0.53	0.42	886.6	9.79	....	58.4	108.1	Diminished sugar
	10:08½–10:29	0.61	0.47	1309.8	9.42	....	95.5	176.8	tolerance
	10:29 –11:29	0.70	0.54	1132.5	8.70	....	95.8	177.3	
	11:29 –12:28½	0.58	0.45	932.9	7.62	....	82.0	151.8	
2	7:22 – 9:22	0.64	....	1271.2	15.44	....	60.0	111.2	100 Gm. dextrose
M. O.	9:22 –10:03	0.67	....	1414.4	15.34	....	68.1	126.2	at 9:22
	10:03 –10:26½	0.89	....	1345.9	14.24	....	80.2	148.6	
	10:26½–10:50	3.89	....	384.2	15.18	81.3	....	108.4	Normal sugar
	10:50 –11:53	8.01	....	149.7	14.91	66.5	....	88.6	curve
	11:53 –12:41	9.89	....	126.1	13.91	74.0	....	98.7	
3	8:30 –10:03	0.65	....	547.6	8.24	....	53.6	99.1	100 Gm. dextrose
F. J. C.	10:03 –11:11½	1.26	....	406.5	8.67	....	52.6	97.3	at 10:03
	11:11½–12:09	1.05	....	430.5	9.07	....	48.6	89.9	Diminished sugar tolerance
4	7:20 –10:01	0.99	0.86	500.5	9.05	....	50.9	94.1	100 Gm. dextrose
J. A. H.	10:01 –10:37	1.59	1.37	486.0	9.13	....	62.3	115.2	at 10:01
	10:37 –11:08	0.71	0.61	578.3	9.44	....	47.8	88.4	Renal glycosuria
	11:08 –12:05	3.31	2.88	278.7	8.72	92.0	....	122.4	Normal sugar
	12:05 – 1.18½	0.16	0.14	733.7	8.69	....	31.2	57.8	curve
5	7:45 – 9:37	0.82	....	534.1	7.14	....	67.8	125.4	100 Gm. dextrose
M. Ba.	9:37 –10:05	1.77	....	354.9	7.29	....	64.7	119.7	at 9:37
	10:05 –10:30	4.72	....	121.1	7.07	80.9	....	107.5	Normal sugar
	10:30 –10:46	1.13	....	410.7	7.53	....	57.8	107.0	curve
	11:47 –12:47	3.33	....	169.3	5.04	112.0	....	148.9	
6	9:45 –10:13½	2.02	....	425.9	10.64	80.7	....	107.6	
M. K.	10:13½–11:25	1.48	....	530.4	9.93	....	64.6	119.6	100 Gm. dextrose at 10:14
	11:25 –12:26½	1.11	....	705.2	10.14	....	73.1	135.2	Normal sugar curve

TABLE 2.—*Summary*

Subject	Number of Observations	Standard Clearance			Maximum Clearance			Percentage of Normal Calculated on Basis of Cs = 54 Cm = 75		
		Average	Maximum	Minimum	Average	Maximum	Minimum	Average	Maximum	Minimum
J. M. H.	6	78.6	95.8	58.4	....	....	....	145.5	177.3	108.1
M. O.	6	69.4	80.2	60.0	73.9	81.3	66.5	113.6	148.6	88.6
F. J. C.	3	51.6	53.6	48.6	....	....	....	95.4	99.1	89.9
J. A. H.	5	48.1	62.3	31.2	92.0	....	....	95.6	122.4	57.8
M. Ba.	5	63.4	67.8	57.8	96.5	112.0	80.9	121.7	148.9	107.0
M. K.	3	68.9	73.1	64.6	80.7	....	....	120.8	135.2	107.6
Mean		63.3			85.8					
Maximum		78.6			96.5					
Minimum		48.1			73.9					
Maximum observed deviation of an individual mean from mean of group		±15			±11					

varied between 48.1 and 78.6 cc. of blood with a mean of 63.3 cc. The average maximum clearances varied between 73.9 and 96.5 cc. with a mean of 85.8 cc. A comparison of the foregoing standard clearances with those recorded in the preceding paper [1] shows that the ingestion of dextrose has little effect on the blood urea clearance. This is in full accord with the observations of Addis and Drury,[3] who studied the effect of the ingestion of 50 Gm. of cane sugar on the urea excretion ratio of Addis,[4] which, as has been mentioned before, is identical with the maximum urea clearance. The average standard clearance is only slightly lower than that in our first series; this is probably due to the subjects' maintenance of the sitting posture. A comparison of the present figures with those of the preceding paper and with those of Möller, McIntosh and Van Slyke [2] shows that the approximately identical percentage of increase in both our average standard and our maximum clearance is probably due to nothing more than our deviation from conditions of absolute rest and not to the effects of the ingestion of dextrose.

In three of our subjects definite diuresis followed the ingestion of the dextrose. In one of these (J. A. H., 4, table 1) the increased output of urine was associated with an increase in the blood urea clearance, but this was not observed in the other two. In fact, one subject (M. O. 2, table 1) tended to show a decrease in the maximum urea clearance with increased flow of urine. Bourquin and Laughton [5] have shown that in dogs diuresis is first associated with an increased urea clearance and that, as the diuresis subsides, the clearance falls. Bruger and Stehle [6] observed during the diuresis resulting from the intravenous injection of 260 cc. of isotonic dextrose into dogs with fistula of the bladder, that the volume of output of urine varies more or less inversely with the urea concentration in the urine. It is impossible to determine the urea clearances from these authors' protocols, since the urea content of the blood was not determined. Assuming a constant blood urea content, their results tend to show an increase in the clearance as the diuresis advances and a fall as the output of urine diminishes. Möller, McIntosh and Van Slyke [2] were unable

3. Addis, T., and Drury, D. R.: The Rate of Urea Excretion: VII. The Effect of Various Other Factors than Blood Urea Concentration on the Rate of Urea Excretion, J. Biol. Chem. **55**:629, 1923.

4. Addis, T.: Renal Function and the Amount of Functioning Tissue, Arch. Int. Med. **30**:378 (Sept.) 1922.

5. Bourquin, H., and Laughton, N. B.: Factors Influencing the Excretion of Urea: II. Diuresis and Caffeine, Am. J. Physiol. **74**:436, 1925.

6. Bruger, M., and Stehle, R. L.: The Effect of Solutions of Dextrose and Various Electrolytes, Intravenously Administered, on the Rate of Secretion and Composition of the Urine, unpublished data.

to verify this in human subjects. In the few cases in which we observed any diuresis following the ingestion of dextrose there was no constant relationship between diuresis and urea clearance. Assuming that diuresis affects the urea clearance, we should expect to find larger deviations of the average clearances from the mean of the group than in cases without any diuretic response, but this was not observed.

COMMENT

In the present series the same wide variations of the urea clearance values are evident as were observed in the persons reported on in the first paper.[1] One case (J. A. H., 4, table 1) is especially noteworthy. The clearance, expressed as a percentage of the normal value, varied between 122 and 58 per cent within two hours. In other words, the ability of the kidney to eliminate urea was more than twice as effective in one hour than it was in the following hour. As was stressed in the previous paper, this is typical of the normal kidney.

On purely physiologic grounds it is conceivable that diuresis may result in an increased excretion of urea per unit of time followed by a diminished output as the diuresis subsides. Urea, as a nonthreshold body, can be subjected to a "washing out" process. As was mentioned, the results of Bourquin and Laughton[5] and of Bruger and Stehle[6] in dogs suggest this. On the other hand, no constant relationship between diuresis and urea clearance has been observed in human subjects. It is probable that the degree of diuresis observed by Van Slyke and his associates and by ourselves in normal persons is not great enough or sufficiently prolonged to affect appreciably the absolute urea content of the body.

SUMMARY

Twenty-eight observations of the urea clearance in six subjects with normal kidneys before and after the ingestion of 100 Gm. of dextrose are reported. The ingestion of dextrose has little or no effect on the blood urea clearance. The degree of diuresis following the ingestion of dextrose in human subjects has little effect on the blood urea clearance.

DIETARY PRACTICES IN RELATION TO THE INCIDENCE OF PELLAGRA

I. A STUDY OF FAMILY DIETARIES IN LEON COUNTY, FLORIDA

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The importance of diet in the prevention and treatment of pellagra is generally accepted. It is not yet clear, however, whether we are dealing with a specific dietary deficiency or whether the deficiency is of a more general nature, important primarily in lowering the body's resistance to disease. Medical opinion in the South is still divided, though the weight of evidence at present available supports the conception of a specific deficiency.

This confusion in our ideas of the relation of diet to the disease is a natural one, in view of the number of theories that have been advanced to explain the relationship. The "spoiled corn" theory, though developed in Italy, was advocated in this country [1] after the recognition of the disease here. While American investigators found no evidence of a specific relation of corn to the incidence of the disease, emphasis on this theory served to confuse the issue and to divert attention from the consideration of other factors in the diet.

The points receiving emphasis during the decade 1910 to 1920 are perhaps illustrated in the work of Siler, Garrison and MacNeal,[2] who studied such problems as the influence of (*a*) cornmeal, homegrown or shipped, sound or decayed, (*b*) the possible injurious effect of the use of canned foods and (*c*) the use of animal protein foods, such as meat, milk and eggs. With emphasis in their studies placed on the possible deleterious effect of the use of cornmeal or canned foods, it is not surprising that they minimized the positive influence of milk which they found, and concluded that diet was less important than domiciliary relationship.

From the School of Home Economics, Florida State College for Women.

1. Marie, A.: Pellagra, translated from the French by C. H. Lavinder and J. W. Babcock, Columbia, S. C., The State Company, 1910. Harris, H. F.: Pellagra, New York, The Macmillan Company, 1919.

2. Siler, J. F.; Garrison, P. E., and MacNeal, W. J.: A Statistical Study of the Relation of Pellagra to the Use of Certain Foods and to the Location of Domicile in Six Selected Industrial Communities, Arch. Int. Med. **14**:293 (Sept.) 1914.

Voegtlin [3] and Goldberger and his associates [4] in the Public Health Service were convinced that diet stood in causal relation to pellagra, but their first experiments, in which they used a liberal mixed diet for prevention or cure, offered no conclusive evidence of a specific deficiency. They [5] suggested the possibility of a protein (or perhaps amino-acid) deficiency, a theory not accepted by all students of the disease, but on which attention was centered for some time. Bigland [6] and Boyd and McLean [7] emphasized the "biological value" of the protein of their diets, almost to the exclusion of other dietary factors, and Jobling and Peterson [8] analyzed their findings in terms of protein requirements, total protein and sources of protein in the diet.

The institutional studies of Goldberger and his co-workers [9] were the first to show under controlled conditions the value of individual food materials in the prevention and cure of pellagra. As, however, the difficulty of work with human subjects has made progress in this direction slow, the production in experimental animals of symptoms which these authors [10] considered analogous to pellagra in human beings

3. Voegtlin, C.: Recent Work on Pellagra, in the Harvey Lectures, ser. 15, Philadelphia, J. B. Lippincott Company, 1920.

4. Goldberger, J.; Waring, C. H., and Willets, D. G.: Treatment and Prevention of Pellagra, U. S. Pub. Health Rep. **29**:2821, 1914; Prevention of Pellagra: A Test of Diet Among Institutional Inmates, ibid. **30**:3117, 1915.

5. Goldberger, J., and Tanner, W. F.: Amino-Acid Deficiency Probably the Primary Etiological Factor in Pellagra, U. S. Pub. Health Rep. **37**:462 (March 3) 1922. Goldberger, Waring and Willets (footnote 4, second reference).

6. Bigland, A. D.: Pellagra Outbreak in Egypt; Pellagra Among Ottoman Prisoners of War, Lancet **1**:947, 1920.

7. Boyd, F. D., and McLean, B. S.: Report of Committee of Inquiry Regarding Prevalence of Pellagra Among Turkish Prisoners of War, J. Roy. Army M. Corps **33**:426 and 508, 1919; ibid. **34**:70; 173 and 272, 1920.

8. Jobling, J. W., and Peterson, W. J.: The Epidemiology of Pellagra in Nashville, Tennessee, J. Infect. Dis. **18**:501 (Jan.) 1916; Epidemiology of Pellagra in Nashville, Tennessee: II., ibid. **21**:109 (Aug.) 1917.

9. Goldberger, J., and Tanner, W. F.: Study of Treatment and Prevention of Pellagra, U. S. Pub. Health Rep. **39**:87 (Jan. 18) 1924; A Study of the Pellagra-Preventive Action of Dried Beans, Casein, Dried Milk and Brewer's Yeast, with a Consideration of the Essential Preventive Factors Involved, ibid. **40**:54 (Jan. 9) 1925. Goldberger, J.; Wheeler, G. A.; Lillie, R. D., and Rogers, L. M.: Further Study of Butter, Fresh Beef and Yeast as Pellagra Preventives, ibid. **41**:297 (Feb. 19) 1926; Goldberger, J., and Wheeler, G. A.: Study of Pellagra Preventive Action of Tomato, Carrot and Rutabaga Turnip, ibid. **42**:1299 (May 13) 1927; Pellagra Preventive Action of Cowpea and Commercial Wheat Germ, ibid. **42**:39, 2383 (Sept. 30) 1927.

10. Goldberger, J.; Wheeler, G. A.; Lillie, R. D., and Rogers, L. M.: Study of Black-Tongue Preventive Action of Sixteen Foodstuffs, with Special Reference to the Identity of Black-Tongue in Dogs and Pellagra of Man, U. S. Pub. Health Rep. **43**:1385 (June 8) 1928.

opens up a fertile field for investigation, with promise of more rapid progress in solution of the problems concerned.

During the last few years, there have been reported a number of cases of pellagra following restrictions in the diet. Carley [11] reported a case of voluntary restriction resulting in the appearance of symptoms of pellagra which cleared up when a liberal mixed diet was prescribed. Eusterman and O'Leary [12] reported 13 cases of the disease secondary to some interference with nutrition, such as restriction in the diet necessitated by lesions or dysfunction of the gastro-intestinal tract. In discussing their cases, Eusterman and O'Leary reviewed the literature of the subject and concluded that this "secondary form of pellagra tends to support the theory that dietary deficiency is the cause of the disease." Crutchfield [13] also, in his analysis of 109 cases of pellagra in the John Sealy Hospital in Galveston, pointed to the number of instances in which the symptoms of the disease developed secondary to some disturbance of nutrition and cleared up when such interfering factors were removed.

Records of the customary dietary practices of pellagrous patients or of families in which pellagra exists are less numerous. Siler, Garrison and MacNeal [2] and Jobling and Peterson [8] considered the relation of diet to the incidence of pellagra as a part of their extensive surveys. Both groups of investigators secured certain information regarding the food habits of all persons and families interviewed, such as the frequency with which certain foods were used and a typical day's menu. In neither case were records secured of the foods actually purchased or consumed. Boyd and McLean,[7] in their report of pellagra in Turkish prisoners of war, gave estimations of the value of the diets previous to capture, based on the statements of the prisoners and their officers. These reports show general tendencies as to consumption of food, but do not furnish quantitative figures.

Goldberger, Wheeler and Sydenstricker [14] were the first, so far as we are aware, to secure quantitative records of family food purchases over a period of time. They secured records of the diets of nonpellagrous and pellagrous households in seven mill villages in South Carolina over a fifteen day period between April 15 and June 15. The records were classified according to family income and pellagrous state,

11. Carley, P. S.: Case of Pellagra Following Voluntary Restriction of Diet, J. A. M. A. **91**:879 (Sept. 22) 1928.

12. Eusterman, G. B., and O'Leary, P. A.: Pellagra Secondary to Benign and Carcinomatous Lesions and Dysfunction of the Gastro-Intestinal Tract: Report of Thirteen Cases, Arch. Int. Med. **47**:633 (April) 1931.

13. Crutchfield, E. D.: Pellagra with Special Reference to the Skin and Mucous Membrane, Arch. Dermat. & Syph. **17**:650 (May) 1928.

14. Goldberger, J.; Wheeler, G. A., and Sydenstricker, E. H.: Study of Diet of Non-Pellagrous and Pellagrous Households, J. A. M. A. **71**:944 (Sept. 21) 1918.

and showed interesting differences in the consumption of milk, fresh meat and vegetables by the nonpellagrous and pellagrous families. Recently, the same group of investigators [15] has published records of food purchases in these same villages during different seasons of the year. The figures indicate considerable seasonal variation in the supply of fresh meat, milk and vegetables available, but are not analyzed to show the relative amounts of these used by pellagrous and nonpellagrous families.

Several writers have suggested that the causes of the disease are probably in operation months before the onset of the usually recognized symptoms. Boyd and McLean [7] postulated a "pre-pellagrous" state on the basis of their studies of the coefficients of digestibility of protein in Turkish prisoners of war. They found a distinct decrease in the individual's ability to use the protein ingested weeks before the appearance of the symptoms on which diagnosis was based. Goldberger, Wheeler and Sydenstricker [14] suggested that the seasonal appearance of pellagra may be correlated with variations in the food supply, if it is assumed that the winter season with its restricted diet serves as a long period of depletion.

NEED FOR FURTHER DIETARY STUDIES

There appears to us to be a need for investigation of the diets of pellagrous persons at different seasons of the year and for comparison of these with diets collected under similar conditions from families free from the disease. Such studies should throw some light on the question of seasonal variation, and should bring into relief any important differences in the dietary practices of pellagrous and nonpellagrous persons.

The present study of family dietaries in Leon County, Fla., has been planned with these considerations in mind, in the hope of securing information concerning (*a*) seasonal variation in the diets of pellagrous families, and (*b*) any important differences in the choice of foods by this group as compared with nonpellagrous families.

METHODS USED IN PRESENT DIETARY STUDY

Selection of Families.—The names of families in which one or more active cases of pellagra existed were secured through the courtesy of local physicians and welfare workers. Only those cases in which diagnosis had been made by a practicing physician were considered. Sixteen such families were found who were willing to cooperate in the study. In fifteen of these, the housewife was pellagrous, and where there were multiple cases of the disease in a family, the additional cases existed among the children. In only one family was the pellagrous member an adult man.

15. Goldberger, J.; Wheeler, G. A.; Sydenstricker, E. J., and King, W. I.: A Study of Endemic Pellagra in Some Cotton Mill Villages of South Carolina, Hyg. Lab. Bull. 153, January, 1929.

For comparison with this group a control group was secured, consisting of thirteen families of similar occupational level who were free from the disease. Many of the families in this second group were friends or acquaintances of the pellagrous group.

The occupations of the principal wage earners in both groups were, in the order of their frequency, those of carpenter, painter, bus or truck driver, small store keeper, mechanic, farmer, fireman and nightwatchman. In two families of each group the principal wage earner reported doing only odd jobs.

Some of the families lived on the outskirts of Tallahassee, a city of about 10,000 inhabitants, while others lived in or near small settlements in the county. None were more than twelve miles from Tallahassee, and the majority came to town on Saturday for the weekly marketing.

Selection of Seasons for Securing Dietary Records.—The seasons selected for collection of the family dietary records were midwinter (January and February), spring (June 1 to 15), late summer (August 25 to September 6) and fall (November 1 to 15), as it was believed that these periods would show the maximum effect of any seasonal influence which might exist. In this district there is seldom killing

TABLE 1.—*Personal Data Concerning Families Studied*

Socio-Economic Factors	Pellagrous Families	Nonpellagrous Families
Number of families reported	16	13
Average number in family	6.7	6
Average weekly money income	$20.10	$28.75
Main wage earner working full time	6	10
Main wage earner working part time	10	3
Families owning home	9	9
Average number of rooms in house	3.5	3.5
Houses with running water	4	5
Houses with sewerage	3	3

frost, and it is possible for the thrifty family to keep a supply of vegetables the year round. The average household, however, does not maintain a garden through the winter months. The great majority of families have a spring garden, which is at its best during May, June and the first part of July. The next two months usually show a decrease in garden produce because of the midsummer heat. The fall gardens are at their height from the middle of September until November or later.

Methods of Securing Information.—The investigator visited the individual families, interviewing the housewife in each case. At the first visit certain personal data covering socio-economic factors were secured. Facts considered pertinent to this study are given in table 1. From this table it will be seen that the two groups were quite similar, though the weekly income of the control group was somewhat larger.

At this first visit an inventory was taken of all foods on hand and records were started jointly by the housewife and the visitor. Record sheets, one for each of the seven days of the experimental period, were left with the housewife to be used for recording purchases or foods otherwise secured on any of these days. Space was provided for giving the name, weight, price and place of purchase, or source, of each article. A second set of sheets was provided for recording the menus for each day. At the end of the seven day period, the investigator returned and checked the market lists and menu sheets to see that all essential information was listed, and to catch and correct any discrepancies between the two records. Foods left

on hand were noted and subtracted from the totals purchased. In general, the women were interested and cooperative, and kept records which were accurate to the best of their ability.

The inventories and market lists were relatively simple affairs, as most of the families marketed once a week and kept little reserve supply on hand.

Throughout the study, the investigator endeavored to maintain a neutral attitude and refrained from making any statements which might influence the family in its choice of food. The physicians diagnosing the cases undoubtedly exerted some influence, as the majority of them made recommendations for the improvement of the diet. This influence was not marked, however, as the limited incomes and meager knowledge of food values made it difficult for the women responsible for the purchase and preparation of the food to make radical changes in their dietary practices.

TABLE 2.—*Number Seasons Represented by Family Dietaries*

Number of Seasons Represented	Total Families	Pellagrous Families	Nonpellagrous Families
4	14	7	7
3	9	6	3
2	4	1	3
1	2	2	0
Totals	29	16	13

TABLE 3.—*Seasonal Distribution of Dietary Records*

	Records Collected at Seasons Specified		
Season	Total	Pellagrous Families	Nonpellagrous Families
January-February	27	15	12
June 1-15	26	14	12
August 27-September 6	21	12	9
November 1-15	19	9	10

At each season the method of securing the food records was the same, and any change in the make-up of the family was noted. Records were kept likewise of the variation in severity of symptoms of pellagra at the different seasons.

RESULTS

A total of ninety-three family dietaries, each covering a period of seven consecutive days, were secured from twenty-nine individual families, sixteen of which had one or more members with active cases of pellagra, while the remaining thirteen families constituted the normal control group. Tables 2 and 3 give the number of seasons for which individual families kept records and the seasonal distribution of these.

The dietary returns have been analyzed in various ways in order that any significant differences in the diets from season to season or from group to group might be brought to light. Table 4 gives the total calories and grams of protein per adult male unit [16] per day for

16. Atwater, W. O.: Principles of Nutrition and Nutritive Value of Food, U. S. Dept. of Agriculture Farmer's Bull., 1918, no. 142, p. 30.

the pellagrous and the control families at each of the four seasons studied. Table 5 shows the distribution of total calories among the food groups, (1) cereals, (2) milk, (3) vegetables and fruits, (4) sweets, (5) fats and (6) animal foods excluding milk. The accom-

TABLE 4.—*Total Calories and Protein Grams Estimated per Adult Male Unit per Day*

Season	Calories per Adult Male Unit per Day		Grams of Protein per Adult Male Unit per Day		Percentage of Total Calories from Protein	
	Pellagrous Families	Non-pellagrous Families	Pellagrous Families	Non-pellagrous Families	Pellagrous Families	Non-pellagrous Families
January-February	3,544	3,985	84.3	100.8	8.8	10.0
June 1-15	4,176	4,001	94.5	96.2	8.9	9.5
August 27-September 6	3,899	3,351	105.2	96.1	10.8	11.1
November 1-15	3,649	4,616	98.0	124.2	10.2	10.4
Average for all seasons	3,817	3,963	95.5	104.3	9.7	10.2

TABLE 5.—*Percentage Distribution of Total Calories Among Food Groups Specified at Different Seasons of the Year*

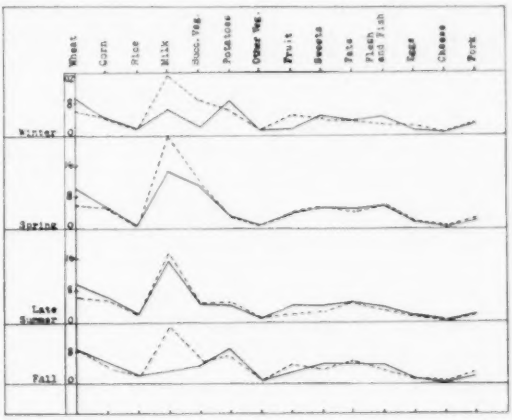
Food Group	Season	Pellagrous Group		Nonpellagrous Group	
		Range, per Cent	Mean, per Cent	Range, per Cent	Mean, per Cent
Cereals	January-February	27.8-58.0	43.3	22.9-43.9	35.6
	June 1-15	31.4-54.7	42.0	26.4-48.1	38.1
	August 27-September 6	18.8-66.6	43.3	25.9-59.5	40.0
	November 1-15	25.0-71.9	40.9	16.7-56.6	33.3
Milk	January-February	0.0-15.2	3.8	2.4-25.2	10.3
	June 1-15	0.0-15.6	5.8	3.1-29.2	11.3
	August 27-September 6	0.0-22.1	5.2	0.0-35.1	9.2
	November 1-15	0.0- 4.0	2.6	1.0-12.0	6.3
Fruits and vegetables	January-February	5.1-15.7	9.5	3.1-20.2	11.2
	June 1-15	2.5-12.9	7.1	2.6- 9.5	6.3
	August 27-September 6	2.3-18.6	7.2	3.0-10.0	7.6
	November 1-15	1.5-20.2	11.0	9.0-18.0	12.6
Sweets	January-February	6.5-18.4	12.3	1.7-16.5	11.3
	June 1-15	3.0-16.0	10.7	6.2-21.7	12.3
	August 27-September 6	1.6-21.7	10.2	0.0-17.8	5.8
	November 1-15	2.5-17.9	10.9	0.0-21.8	9.1
Fats	January-February	7.0-32.4	19.6	8.8-31.7	20.6
	June 1-15	16.3-36.6	27.1	13.6-39.2	23.4
	August 27-September 6	4.8-44.6	23.2	0.0-43.4	23.9
	November 1-15	11.0-42.2	20.6	15.8-44.0	28.9
Animal foods except milk	January-February	2.2-29.7	11.8	1 3-21.0	12.6
	June 1-15	0.0-13.2	6.7	2.0-22.9	8.9
	August 27-September 6	0.0-24.6	9.0	2.2-25.2	7.6
	November 1-15	2.6-22.5	11.8	0.0-19.2	9.8

panying chart presents graphically the distribution of the total food supply in ounces per adult male unit per day for the pellagrous and the nonpellagrous families at each season, and table 6 gives calculations of the differences in the use of certain foods by the two groups.

It may be seen from table 4 that calories are liberal and total protein within normal limits for both groups. Household waste probably accounts, in part, for the apparent high calorie value of the diets.

The first important difference which appears is in the use of milk. In table 5 this difference is evident. When the amounts are expressed in ounces per adult male unit per day, as in table 6, the difference is marked, being almost three times the probable error in the winter diets and over five times the probable error in the fall diets.

A second difference of almost equal importance appears in table 6, in the use of succulent vegetables by the two groups. In the winter diets the difference in favor of the nonpellagrous families is more than three times the probable error, while in the fall records it is more than two. This difference is masked in table 5 by the inclusion of potatoes in the vegetable group.



Graph of the food supply of nonpellagrous and pellagrous families at different seasons of the year, estimated in ounces per adult male unit per day. Pellagrous families, ——; nonpellagrous, - - - -.

The use of cereals by the pellagrous families seems somewhat greater than that by the control families. The chart shows that wheat was used to a greater extent than corn, and that the latter was used in about the same amount by both groups. There is some indication of a difference in the amounts of eggs, cheese and fruit used, but the individual differences are too great for this to be more than suggestive. The amount of fats and sweets used is very similar in both groups. The same is true of the use of flesh and fish, a result somewhat different from that which the experience of earlier investigators [14] would lead one to expect.

Both table 6 and the chart show seasonal variation in the supply of milk and succulent vegetables, a variation that is greater in the pellagrous than in the nonpellagrous diets. It would seem that the food supply

TABLE 6.—*Supply of Certain Foods per Adult Male Unit per Day for Different Seasons of the Year*

	Ounces per Adult Male Unit per Day at Specified Seasons											
	Winter			Early Summer			Late Summer			Fall		
	Pellagrous Group	Non-pellagrous Group	Difference	Pellagrous Group	Non-pellagrous Group	Difference	Pellagrous Group	Non-pellagrous Group	Difference	Pellagrous Group	Non-pellagrous Group	Difference
Cereals	15.65	13.62	2.03 ± 1.10	17.54	14.08	3.46 ± 1.50	18.43	13.40	5.03 ± 1.44	16.14	14.53	1.61 ± 1.96
Milk	6.85	15.87	9.02 ± 3.32	14.83	23.03	8.20 ± 4.90	15.01	16.95	1.94 ± 3.35	3.34	14.66	11.32 ± 2.70
Succulent vegetables	2.05	8.80	6.75 ± 2.15	10.87	11.53	0.66 ± 1.51	4.30	5.88	1.58 ± 0.90	4.13	6.79	2.66 ± 1.14
Potatoes	9.22	6.26	3.96 ± 1.56	3.06	3.23	0.17 ± 0.23	4.00	4.69	0.69 ± 1.02	8.34	8.50	0.16 ± 1.61
Fruit	1.29	4.80	3.51 ± 1.48	3.82	3.26	0.56 ± 1.10	3.51	1.33	2.18 ± 1.30	2.30	4.05	1.75 ± 1.30
Eggs	0.95	1.71	0.76 ± 0.31	1.49	1.55	0.06 ± 0.49	0.85	0.92	0.07 ± 0.56	0.76	1.05	0.29 ± 0.50
Cheese	0.08	0.27	0.19 ± 0.11	....	0.45	.....	0.09	0.11	0.02 ± 0.10	0.05	0.17	0.12 ± 0.10
Flesh and fish (except pork)	4.44	2.86	1.58 ± 0.74	5.23	5.61	0.38 ± 1.37	3.43	2.97	0.46 ± 0.88	4.66	3.63	1.03 ± 1.21
Pork, lean	2.42	2.38	0.04 ± 0.57	0.90	1.38	0.48 ± 0.43	1.31	0.27	1.04 ± 0.76	1.82	2.03	0.21 ± 0.71

of the pellagrous group is more influenced by fortuitous circumstances than is that of the nonpellagrous families. When the food supply is abundant, the pellagrous family has a more liberal diet, but when the season is less favorable, little effort seems to be made to keep the diet uniform.

Records of recurrences of pellagra in the families studied show that the eruption appeared most frequently in March and April, before the increased food supply of the spring was available.

COMMENT

Milk has long been recognized as valuable in the prevention and treatment of pellagra. Roussel,[17] as early as 1845, stated that the most effective treatment of pellagra was a milk diet. Goldberger, Waring and Willets,[18] in their studies of institutional diets, found that an inverse relation existed between the use of milk and the incidence of the disease. Goldberger and Tanner [19] presented definite evidence of the value of whole milk, butter milk and dry skim milk in prevention and treatment of the condition. Siler, Garrison and MacNeal [2] found "that the families in which milk was not used were the ones in which pellagra appeared the most frequently, while on the other hand, those families using this food daily developed new cases the most infrequently." Wheeler [20] cited three cases to show that "in cases of borderline nutrition, where a slight unfavorable change in diet may put the family into the malnourished class, the milk supply may be the controlling factor in the appearance or non-appearance of the disease."

The present study confirms the earlier observations of an inverse relationship between the use of milk and the incidence of pellagra, and extends these findings in showing the existence of a seasonal variation in the milk supply of the families studied, which is sufficiently greater in the pellagrous diets to constitute a significant difference between the dietary practices of the two groups.

The seasonal variation in the use of succulent vegetables found in this study confirms the general observations to this effect, and here again extends earlier observations in showing that the variation is greater in the pellagrous families. We do not have as yet sufficient knowledge of the relative merits of individual vegetables to be able to discuss the importance of this variation in terms either of pellagra

17. Roussel, cited in McCollum, E. V., and Simmonds, N.: Newer Knowledge of Nutrition, ed. 3, New York, The Macmillan Company, 1925, p. 321.

18. Goldberger, Waring, and Willets (footnote 4, first reference).

19. Goldberger and Tanner (footnote 9, first reference).

20. Wheeler, G. A.: Pellagra in Relation to Milk Supply in Households, U. S. Pub. Health Rep. **39**:2197 (Aug. 29) 1924.

preventive, blacktongue preventive or vitamin G values. There is no doubt, however, that the general nutritional value of the monotonous and limited dietaries would be improved by the liberal and uniform use of these foods.

A study of twenty-nine families is too limited in scope to warrant generalizations. The results, however, would seem to justify emphasis, in practical dietary recommendations, on the need for an increased use of succulent vegetables during the months when garden produce is less plentiful and for the establishment of a uniformly liberal milk supply throughout the year.

SUMMARY AND CONCLUSIONS

1. A study has been made of the dietaries of twenty-nine families in Leon County, Fla. Active cases of pellagra existed in sixteen of these, while the members of the remaining thirteen families were free from the disease. Dietary records to the number of ninety-three, each covering a period of seven days, have been collected at different seasons of the year, namely, midwinter, spring, late summer and fall.

2. Comparison of the records of the pellagrous and the control groups shows significant differences in the use of milk and succulent vegetables, particularly in the fall and winter diets, with some indications of a difference in the use of eggs, cheese and fruit. The use of lean meat and fish is similar in both groups.

3. Evidence of a distinct seasonal variation in the supply of milk and succulent vegetables is presented, which confirms the observations of previous investigators and extends their findings in showing that this seasonal influence is sufficiently more marked in the dietaries of the pellagrous families to constitute an important difference in the dietary practices of the two groups.

UNDULANT FEVER

AN EPIDEMIC OF SUBCLINICAL INFECTION WITH BRUCELLA

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In recent years, so much has been written about infection with Brucella that it seems advisable to limit this report to the briefest and most objective description of my own experience. For excellent reviews, with bibliographies, the reader is referred to the publications of Hardy [1] and of Löffler,[2] and to the report of the League of Nations.[3]

The persons dealt with in this study were the pupils, masters and employees in a boys' boarding school in a rural region of Connecticut, where I have been in continuous resident attendance for the past three years. Excellent hospital equipment, with adequate nursing care, and laboratory facilities, with technical assistance, are an integral part of the school. Individual medical records with notation of every complaint, however trivial, are carefully kept. During the winter term, each boy is briefly examined every day, and during the rest of the school year frequent examinations are made. This close personal supervision, together with the laboratory facilities available, creates an opportunity for clinical observation that is almost unique.

For many years, the entire milk supply of the school has come from the school dairy, containing about a hundred Holstein cows. In 1925, there was an epidemic of contagious abortion in this herd, about a dozen cows losing their calves prematurely. Apparently, there was no reflection of this bovine epidemic in the general health of the members of the school community at that time. As there had been no sign of infection in the herd in five years, it was assumed that the herd was free from the disease, and the milk was rated as certified, grade A milk.

Because raw milk was being used in the school, a serum agglutination test for Brucella was tried on nearly every boy who entered the infirmary with fever, no matter what the apparent cause. Furthermore, a number of agglutination tests were made on boys who had not been sick, as I was interested in finding the incidence of agglutinins in normal per-

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1. Hardy, A. V.: Undulant Fever, Washington, D. C., National Institute of Health Bull. 158, Dec., 1930.

2. Löffler, W.: Febris undulans Bang des Menschen, Würzb. Abhandl. a. d. Gesamtgeb. d. Med. **26**:365, 1930.

3. Epidemiol. Rep., League of Nations **9**:409 (Oct. 15) 1930.

sons who had been drinking large quantities of raw milk. As all of these tests were negative prior to Nov. 27, 1930, it is known definitely that agglutinins developed in a considerable number of boys within a certain period. Suddenly, on November 27, a boy fell sick with a severe febrile illness which was diagnosed as undulant fever; this case has been reported elsewhere.[4] As soon as this diagnosis was established, the herd was reinvestigated. It was found that one cow had dropped a pair of weak twin calves a few days before time, on November 13. Her milk was first used on November 18. This cow and four others of the herd were found to give positive reactions when their serums were tested for agglutinins with an antigen made from four strains of Brucella of bovine origin. Only three of the five cows were fresh at the time. These three had Brucella agglutinins in their whey also, but only the one that had calved prematurely was shedding Brucella organisms in her milk, so far as one could tell by inoculations of guinea-pigs. These cows were removed from the herd. Pasteurization of the milk at 63 degrees C. for thirty minutes was started as soon as possible. No raw milk was used after December 20.

Many serum agglutination tests for Brucella had been done in the preceding year, but with the finding of a case of undulant fever in the student body, an intensive serum study was begun. From Dec. 1, 1930, to Dec. 1, 1931, 232 boys between the ages of 13 and 19 and 31 young adults were studied for the presence of serum agglutinins. All of these persons had been drinking large quantities of the infected milk for at least three months, and some had been drinking it for several years. With the exceptions to be noted, none of these persons had had any contact with animals. At least three separate routine agglutination tests were made on each person, while dozens of tests were made on some.[5] Blood cultures were made on each person studied,

4. Dooley, P.: Undulant Fever, New England J. Med. **204**:759 (April 9) 1931.

5. In the school laboratory the technic for the agglutination test was essentially the same throughout this work. The organisms were grown for forty-eight hours on beef liver infusion agar, then washed off with physiologic solution of sodium chloride to which 0.1 per cent formaldehyde had been added. This antigen was diluted to 1:1,000 (silica standard, given in Standard Methods of Water Analysis, ed. 6, New York, American Public Health Association, 1925, p. 4). Unheated serum was used in dilutions of from 1:10 to 1:320, higher dilutions being used on positive serums. The final readings were made after twenty-four hours: eight in the incubator at 37 C. and sixteen in the icebox between 5 and 15 C. The titers recorded indicate the maximum dilution in which there was complete clearing of the supernatant fluid. It was found that the titer curve for any given specimen varied with the dilution of the antigen, but did not vary appreciably with antigens made from the various strains isolated in the course of this study.

Several examinations of the stools and duplicate serum agglutination tests on more than 100 subjects were made in the laboratories of the Connecticut State

and were repeated if agglutinins were found in the serum. Unless there were clinical suggestions of disease, cultures of the stools and urine were made only on persons whose serums agglutinated above 1:160. Daily records of temperature were kept for all persons who showed agglutinins. Monthly weight charts were kept for all persons in the group. When a boy thus observed showed neither loss of weight nor failure to gain in weight and had no fever and no history of lassitude, weakness, malaise, sweating, chilliness, loss of appetite, nervousness, cough, headache, backache, abdominal pain or constipation, it seemed safe to say that he had not had undulant fever, no matter how high his agglutinin titer against Brucella organisms may have been. Furthermore, when fever and signs of infection of the upper respiratory tract developed in a boy, at a time when other boys, without such agglutinins,

TABLE 1.—*Results of Agglutination Tests*

Greatest Dilution of Complete Agglutination During Study	Number of Persons Tested	Percentage of Persons Tested	Number of Persons Who Had Any Form of Febrile Illness	Percentage Who Had Such Illness
Negative	155	58.7	57	37
1:10 to 1:40	62	41.3	17	34
1:80 to 1:160	32		13	
1:320 to 1:640	6		3	
1:1,280 to 1:2,560	5		1	
1:5,120 to 1:12,000	4		3	

showed the same signs and reacted in the same way, it seemed unreasonable to relate his illness to Brucella infection, no matter how high his agglutination titer may have been.

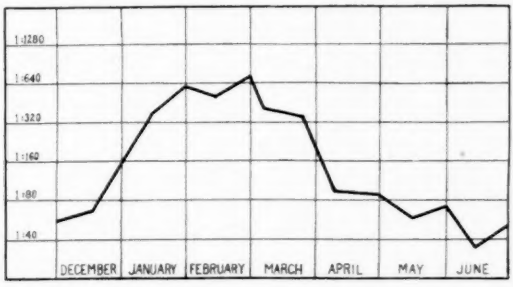
The results of the study of agglutination are shown in table 1, in which it will be seen that 41.3 per cent of the persons studied showed agglutinins against Brucella in some dilution. The fact that a group of young children who used this same milk showed no serum agglutination has been discussed elsewhere.[6] Table 1 presents a statistical artefact, as the tests were not done on all of the group simultaneously but at various times over six months. Doubtless, a number of persons who showed relatively low titers would have had higher ones had they been tested earlier. Enough persons were tested frequently over

Department of Health by permission of Mr. F. L. Mickle. Dr. Elizabeth Parsons, director of laboratories of the West Virginia State Department of Health, identified some of the strains of Brucella isolated from patients and carried out numerous duplicate agglutination tests. Brucella strains isolated in the school laboratory were identified serologically, by agglutinin absorption, as Abortus, with the help of Dr. R. E. Dyer of the National Institute of Health.

6. Dooley, P.: Incidence of Undulant Fever in Children, Arch. Dis. Childhood **6**:235 (Aug.) 1931.

this period to make it certain that the height of the epidemic, so far as agglutinin titers are concerned, was in January and February, and that there was a general decline in the ensuing three months (chart 1). In any case, the possibility of error lies in placing persons in a low titer group who may well have had much higher titers earlier.

Two persons had definite undulant fever, as evidenced by the clinical course, the finding of Brucella organisms in the blood and stools and the presence of serum agglutinins. Their serum titer curves over one year are shown in table 2, in which they are listed as cases 1 and 2. Five other persons (cases 3 to 7, table 2) had infections of the upper respiratory tract with fever at some time during the year, these febrile infections in association with high serum titers suggesting undulant fever even though the other laboratory findings and the clinical courses



The average titer of agglutination tests by two week periods. In a crude way, this indicates the course of the infection in terms of agglutinin formation.

did not suggest that diagnosis. If one may assume that the time of exposure began with the use of the milk from the one cow, the first case occurred on the tenth day after the first exposure and the second case on the thirtieth day after the first exposure and the seventh day after the last exposure. The incubation period for this disease has been variously estimated at from three days to three weeks. Apparently it was ten days in the first case and an indeterminate time in the second. The doubt as to whether the condition in the other cases is to be considered as undulant fever is so great as to permit no conclusions about the incubation period. The patients in cases 8 to 15 (table 2) had no illness and did not show Brucella organisms in the blood, stools or urine at any time, despite the fact that repeatedly verified serum agglutination tests were positive in high dilutions (1 : 5,120 in 2 cases). These findings are presented because they seem to indicate that persons can be infected with Brucella and yet give no clinical evidence of such

TABLE 2.—*Serum Agglutination of Persons Whose Serum Gave a Positive Reaction in the Dilution of 1:320 at Any Time During the Study*

	1930				1931									
Case	March	May	October	December	January	February	March	April	May	June	September	October	November	December
1	.....	.....	Negative	1:2,560	1:12,000	1:5,120	1:1,280	.....	.....	1:160	Negative	.....	.....	Negative
2	.....	.....	.....	.....	1:2,560	1:5,120	.....	1:320	.....	1:80	.....	.....	.....	.....
3	.....	.....	.....	.....	1:1,280	1:2,560	.....	.....	1:640	.....	1:80	.....	.....	1:20
4	Negative	.....	.....	.....	.....	.....	1:640	.....	.....	1:640	.....	1:80	.....	1:80
5	.....	.....	.....	.....	1:100	1:640	.....	.....	.....	1:80	.....	.....	Negative	.....
6	.....	.....	.....	.....	.....	1:320	.....	.....	1:120	.....	.....	.....	.....	Negative
7	.....	.....	.....	.....	.....	1:5,120	1:5,120	1:2,560	1:1,280	1:640	.....	.....	.....	.....
8	.....	Negative	.....	.....	1:2,560	1:5,120	1:2,560	1:640	1:320	1:320	1:120	1:120	.....	1:120
9	.....	.....	.....	.....	.....	.....	1:2,560	.....	.....	1:1,280	.....	1:120	.....	.....
10	.....	.....	.....	.....	.....	.....	.....	.....	1:320	1:320	.....	.....	1:120	.....
11	.....	.....	.....	.....	.....	.....	.....	1:1,280	.....	.....	.....	1:120	.....	.....
12	.....	.....	.....	.....	.....	.....	.....	1:1,280	.....	1:320	.....	.....	.....	Negative
13	.....	.....	.....	1:40	.....	.....	.....	1:640	.....	1:120	.....	.....	.....	.....
14	.....	.....	.....	.....	1:1,280	.....	1:320	.....	.....	1:20	Negative	.....	.....	Negative
15	.....	.....	.....	.....	.....	.....	.....	1:640	.....	1:320	.....	1:20	.....	1:20

infection, King and Caldwell,[7] Hardy,[1] Hasseltine,[8] Huddleson and Johnson [9] and Jordan [10] have recorded studies in which this seemed true.

In an isolated and closely associated group of persons such as this one, minor epidemics of infection of the upper respiratory tract with fever recur throughout the year. One wonders whether persons with agglutinins against Brucella are more susceptible to such infection than those without agglutinins. In table 1, it appears that 34 per cent of those with agglutinins had some form of febrile illness, while 37 per cent of those without agglutinins had such illness. Comparison of the individual records of those with infection of the upper respiratory tract shows that the average duration of illness was approximately the same in the two groups. The figures for the incidence of respiratory infection include the entire year and not just the period of the study of agglutination recorded in the rest of the table.

In 11 boys who on several occasions had been found to have positive agglutination tests against Brucella in low dilutions (1 : 10 to 1 : 40) febrile illnesses developed which could not be confused with undulant fever, however atypical. These illnesses included pertussis, varicella, follicular tonsillitis due to beta-hemolytic streptococci, serum sickness and reaction to typhoid vaccine. Seven of these boys showed a quick increase in serum agglutinins, in one instance an increase from 1 : 80 to 1 : 640 in one week. Apparently fever due to any cause may increase serum agglutinins against Brucella, whether the person has or has not had a clinical infection with undulant fever in the past. These findings make one particularly cautious in accepting the diagnosis of undulant fever whenever a fever of unknown etiology is associated with a positive agglutination test, even when the titer is high. Apropos of this, Gilbert and Coleman,[11] working with typhoid fever, concluded that "fluctuation of the agglutinin titer, considered by some as definite evidence of typhoid infection, may occur in cases in which this infection is definitely excluded."

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7. King, M. J., and Caldwell, D. W.: Undulant Fever, Am. J. M. Sc. **178**: 115, 1929.

8. Hasseltine, H. E.: Study of the Epidemiology of Undulant Fever, Am. J. Pub. Health **21**:519 (May) 1931.

9. Huddleson, I. F., and Johnson, H. W.: Brucellosis, J. A. M. A. **94**:1905 (June 14) 1930.

10. Jordan, C. F.: Infection in the Epidemiology of Undulant Fever in the General Population and in Selected Groups in Iowa, J. Infect. Dis. **48**:526 (June) 1931.

11. Gilbert, R., and Coleman, M. B.: Agglutination of Typhoid Bacilli of Patients Having Unrelated Infections, J. Infect. Dis. **46**:311 (April) 1930.

As many cases of undulant fever have been reported as the result of laboratory infection, it is worth noting that neither of the technicians, who handled cultures and live antigens almost daily for more than a year, showed agglutinins in their serums. One of them had used none of the raw milk; the other, very little of it. Of the entire group, the four dairymen, all of whom had negative serum, are the only ones who ever came in contact with animals.

Perhaps the most significant feature of this study has been the finding of agglutinins in persons who could not have had undulant fever. Under certain conditions, perhaps whenever small quantities of Brucella organisms of relatively low virulence are ingested over long periods, antibodies develop in the absence of undulant fever. The protean character of the clinical manifestations of undulant fever is so generally appreciated that there may be a tendency to call any illness undulant fever when there are agglutinins in the patient's serum. It appears that one must be cautious in making this diagnosis in clinically atypical cases unless the organism can be recovered.

SUMMARY

Forty-one per cent of 263 persons using infected raw milk were found to have serum agglutinins against Brucella abortus.

Of those whose serums agglutinated in the dilution of 1:320 or above two had clinical undulant fever, five had febrile illnesses other than undulant fever and eight had no illness.

LOW VOLTAGE IN THE ELECTROCARDIOGRAM

OCCURRENCE AND CLINICAL SIGNIFICANCE

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In the course of the routine interpretation of electrocardiograms, records are frequently encountered in which the Q-R-S complexes are small. The condition is called "low voltage" when the greatest excursion is less than 5 mm. in amplitude in all three leads.[1] It is not uncommon. At the Presbyterian Hospital it was found thirty-one times in the last thousand records, an incidence of 3 per cent. Despite the frequency of this electrocardiographic abnormality, a review of the available literature leaves its significance uncertain. Because of the doubt covering its interpretation, the cases of low voltage at this hospital have been reviewed with the hope of gaining further insight into the occurrence and clinical significance of this deviation from the normal electrocardiogram.

REVIEW OF THE LITERATURE

Waves of low amplitude were first noted as a part of the electrocardiographic picture in the disturbance of intraventricular conduction formerly called "arborization block."[2] Low voltage was also described in hypothyroidism, in which condition it tended to disappear as the basal metabolism returned toward normal with appropriate therapy.[3] The

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1. Criteria for the Interpretation of Electrocardiograms, New York, New York Tuberculosis and Health Association, 1931. Some authors have adopted less rigid standards and have said that low voltage was present when the complexes were less than 5 mm. in amplitude in one or two leads only, or even when the greatest excursion was less than 1 cm. In the present paper the arbitrary but more commonly accepted criterion has been adhered to, as stated.

2. Carter, E. P.: Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborizations: Clinical and Histologic Report of a Case in Which Such Aberrant Complexes were Obtained, Arch. Int. Med. **22**:331 (Sept.) 1918. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic Changes Associated with Myocardial Involvement: With Special Reference to Prognosis, J. A. M. A. **69**:429 (Aug. 11) 1917; The Value of the Electrocardiogram in the Diagnosis and Prognosis of Myocardial Disease, Tr. A. Am. Physicians **39**:247, 1924.

3. Zondek, H.: Das Myxodemherz, München. med. Wchnschr. **65**:1180, 1918. Thacher, C., and White, P. D.: The Electrocardiogram in Myxedema, Am. J. M. Sc. **171**:61, 1926. Reid, W. D., and Kenway, F. L.: Electrocardiographic Signs Associated with Low Basal Metabolism, Endocrinology **13**:191, 1929.

work of a number of German investigators has shown that in these cases the electrocardiographic finding is the result of an increased electrical capacity of the skin and is not due to a fundamental change within the muscle of the heart.[4]

A decrease in the venous flow to the heart or a change in cardiac position has been noted to cause a lowering of the voltage.[5] In both clinical and experimental pericardial effusion low voltage may be present.[6] Low voltage has been associated by some authors with definite cardiac disease.[7] Sprague and White, in 1926, reported a series of fifty-seven cases from the Massachusetts General Hospital.[8] From their study of this series the authors concluded that low voltage was of serious prognostic import, and that it did not occur in electrocardiograms of normal hearts. Hepburn and Jamieson,[9] in the same year, reached similar conclusions. The series reported by these authors differed from that of Sprague and White in that all cases showing evidence of myocardial damage or such abnormalities of mechanism as auricular fibrillation were excluded. In the following year, Willius, from a review of the material at the Mayo Clinic, reached the conclusion that low voltage, in the absence of other abnormalities in the electrocardiogram, was of no significance.[10] These two conflicting views dominate the literature.

4. Lueg, W.: Haut und Elektrokardiogramm, Arch. f. d. ges. Physiol. **212**: 649, 1925; Ueber das Elektrokardiogramm des Myxodems, Ztschr. f. klin. Med. **104**:337, 1926; Ueber das Elektrokardiogramm des Myxodemherzens, Deutsche med. Wchnschr. **53**:319, 1927; Elektrochemische Untersuchungen der menschlichen Haut, Ztschr. f. klin. Med. **106**:21, 1927. Nobel, E.; Rosenbluth, A., and Samet, B.: Das Elektrokardiogramm des kindlichen Myxodems, Ztschr. f. d. ges. exper. Med. **43**:332, 1924.

5. Otto, H. L.: Effect of Altering Venous Inflow to the Heart on the Voltage of the Electrocardiogram, Proc. Soc. Exper. Biol. & Med. **26**:202, 1928; Effect of Altering Position of the Heart on the Voltage of the Electrocardiogram, ibid. **26**:204, 1928.

6. Katz, L. N.; Feil, H. S., and Scott, R. W.: The Electrocardiogram in Pericardial Effusion: II. Experimental, Am. Heart J. **5**:77, 1929. Oppenheimer, B. S., and Mann, H.: An Electrocardiographic Sign in Pericardial Effusion, Proc. Soc. Exper. Biol. & Med. **20**:431, 1923.

7. White, P. D., and Burwell, C. S.: The Clinical Significance of Changes in the Form of the Electrocardiogram, M. Clin. North America **4**:1839, 1921. Pardee, H. E. B., and Master, A. M.: Electrocardiograms and Heart Muscle Disease, J. A. M. A. **80**:98 (Jan. 13) 1923. Master, A. W., and Pardee, H. E. B.: The Effect of Heart Muscle Disease on the Electrocardiogram, Arch. Int. Med. **37**:42 (Jan.) 1926. Burnett, C. T., and Piltz, G. F.: Low Voltage in the Electrocardiogram, Am. Heart J. **2**:649, 1927.

8. Sprague, H. B., and White, P. D.: The Significance of Electrocardiograms of Low Voltage, J. Clin. Investigation **3**:109, 1926.

9. Hepburn, J., and Jamieson, R. A.: The Prognostic Significance of Several Common Electrocardiographic Abnormalities, Am. Heart J. **1**:623, 1926.

10. Willius, F. A., and Killins, W. A.: The Occurrence and Significance of Electrocardiograms of Low Voltage, Arch. Int. Med. **40**:332 (Sept.) 1927.

As a possible explanation of the mechanism of low voltage, Wilson [11] has recently pointed out "that any increase in the conductivity of the body tissues, particularly of those tissues which lie in close proximity to the heart, will decrease the amplitude of the electrocardiographic deflections. . . . The question arises, therefore, as to whether edema of the lungs, pericardial effusion, hydrothorax, ascites or massive edema of all the body tissues may not decrease the amplitude of the electrocardiographic deflections." In such an event it would seem that the prognosis of a given case should be independent of the electrocardiographic finding and dependent entirely on such factors as the degree of cardiac insufficiency and the type of heart disease. Other authors have suggested or hinted that the cause of low voltage might be present within the muscle of the heart itself; i. e., that a poorly functioning myocardium might be incapable of producing enough difference in electrical potential at the surface of the body to produce waves in the electrocardiogram of normal amplitude.

MATERIAL

Low voltage was present in the electrocardiograms of 194 patients who entered the Presbyterian Hospital between 1921 and 1930. For the purposes of this study the histories of these cases have been analyzed. The electrocardiographic records in which low voltage occurred were examined, and the standardization of each lead was determined to be correct; i. e., the introduction of 1 millivolt of current produced a deflection of the string of 1 cm. Low voltage was said to be present when the greatest deflection of a properly standardized string was less than 5 mm. in all of the three standard leads. All cases of low voltage were included regardless of whether there were or were not other coincident electrocardiographic abnormalities. That such a step was justifiable may be seen from the details of the analysis to be presented. It was found necessary to exclude 30 cases from the group because of inadequate clinical data. This left a series of 164 cases for analysis.

The 164 cases fell readily into 2 large groups: In the first were 113 patients with various forms of heart disease. In the second group were 51 patients with a multiplicity of diseases, which will be considered in detail.

OCCURRENCE OF LOW VOLTAGE IN PATIENTS WITH HEART DISEASE

The 113 patients in this series were subdivided into the following groups:

Group I: Patients with Heart Disease with Congestive Failure.—Sixty-three of the 113 patients with heart disease presented symptoms

11. Wilson, F. N.: The Distribution of the Potential Difference Produced by the Heart Beat Within the Body and at Its Surface, Am. Heart J. **5**:599, 1930.

and signs of slight to severe cardiac insufficiency, including the presence of abnormal distribution of fluid, varying from slight edema to general anasarca. There were 38 male and 25 female patients. The age range was from 13 to 80 years, with an average age of 53. On the basis of etiology, the cases were divided as follows: arteriosclerotic heart disease (including hypertension), 40; rheumatic, 17; syphilitic, 5; unclassified, 1.

In these cases low voltage appeared to be closely associated with congestive failure, was present only when combined with congestive failure, but was not invariably present when congestive failure appeared. In the electrocardiograms of fifty-four patients there was evidence of myocardial damage or of a disorder of the cardiac mechanism in addition to the low voltage. In only nine cases was low voltage the only abnormal finding.

Only a single electrocardiogram was taken in each of sixteen cases. In the remaining forty-seven cases there were two or more records. In thirty-three of the forty-seven cases the low voltage was a transient phenomenon, almost invariably occurring in the first records taken after admission and disappearing with the restoration of compensation. In six cases this sequence was reversed, and the low voltage, while absent in the initial electrocardiograms, appeared as a terminal finding at a variable period before death. In eight patients who were more or less decompensated throughout their period of observation, low voltage was a constant finding.

The following cases are typical examples of this group:

CASE 1.—G. K., a white woman, aged 45, entered the hospital on Oct. 2, 1929, because of cardiac decompensation. The diagnosis was arteriosclerotic heart disease with hypertension, cardiac hypertrophy and auricular fibrillation. In an electrocardiogram taken on the day of admission the voltage was low. Additional findings were auricular fibrillation, inversion of T_1 and left axis deviation. The patient was digitalized and responded with a most satisfactory and rapid clinical improvement accompanied by a marked diuresis. A second electrocardiogram taken two days after admission showed that the low voltage had disappeared; in a third record taken five days later it had not recurred.

This is an example of low voltage present as a transient finding in a patient decompensated on admission to the hospital and disappearing with restoration of compensation. In the next case, low voltage occurred as a terminal event.

CASE 2.—A. J., a white man, aged 59, was admitted to the hospital on Feb. 20, 1925, with a diagnosis of arteriosclerotic heart disease, cardiac hypertrophy, auricular fibrillation and moderate cardiac insufficiency. An electrocardiogram taken on admission showed waves of normal amplitude, auricular fibrillation and a disturbance in the intraventricular conduction. Despite rest and the administration of digitalis, the course was rapidly downhill, with increasing decompensation. Ten

days after admission a second electrocardiogram again showed normal voltage. Three weeks later low voltage had appeared. By this time the patient was irrational and was transferred to another hospital, where, shortly afterward, he died.

In the following case low voltage was "permanent" in the sense that it was present on admission and persisted to the death of the patient.

CASE 3.—J. B., a white man, aged 53, suffering from arteriosclerotic heart disease, was admitted to the hospital because of marked cardiac decompensation. The electrocardiogram taken on admission showed a few ventricular extrasystoles and low voltage. On the tenth day low voltage was again present, as was the case on the seventeenth day. There was no improvement in the patient's condition, and he died on the twenty-third day in the hospital.

Group II: Patients with Heart Disease Without Congestive Failure.—In this group there were forty-three patients. In none of these cases was there clinical evidence of congestive failure nor did x-ray pictures, which were taken in many instances, reveal evidence of pleural or pericardial effusions. All the patients had definite organic heart disease. Pain was the presenting symptom in many. There were twenty-nine male and fourteen female patients in this group. The age range was from 18 days to 79 years, with an average age of 54 years.

Classified according to etiology, thirty-three cases belonged to the group with arteriosclerotic heart disease, eight patients had rheumatic heart disease, and there was one case each of syphilitic and of congenital heart disease. Evidence of associated myocardial damage or a disorder of the cardiac mechanism such as auricular fibrillation was present in addition to low voltage in the electrocardiograms of thirty patients. In thirteen cases low voltage was the only finding of importance. This latter figure is notably higher than that for the group with congestive failure.

As to the duration of low voltage, it is unfortunate that in twenty of the forty-three cases in this group only one record was taken. In seventeen instances low voltage was a transient phenomenon, differing, however, from its occurrence in the group with congestive failure in that it was not so strikingly confined to the initial record or to the first few records after admission. In fact, the contrary was apt to be the case, and low voltage usually occurred sporadically through a series of electrocardiograms on a given patient. For instance, in one patient the first three records during an admission to the hospital showed waves of normal amplitude, the next two showed definite low voltage, and the next two were again normal. Or, again, this sequence was seen: normal voltage in the first record, low voltage in the second and a return to normal in the next two.

In only one case did low voltage appear for the first time as a part of the terminal events. Where two or more records were taken, low voltage was constantly present in five patients.

An example of the occurrence of low voltage in this group is presented in the following case:

Case 4.—G. S., a white woman, aged 70, was admitted to the hospital a few days after a coronary occlusion. Physical examination revealed no evidence of decompensation. The patient's chief complaint was cardiac pain that had been persistent from the onset of the occlusion, but was diminishing in severity. An electrocardiogram taken two days after admission showed only low voltage. Three days later the pain had disappeared entirely, the patient was comfortable, and the electrocardiogram was normal. A third record taken eleven days later, on her sixteenth day in the hospital, was again normal. On the seventeenth day, a second coronary thrombosis occurred. An electrocardiogram taken on the twenty-first day showed a recurrence of low voltage. No subsequent records were secured.

Group III: Patients with Heart Disease not Included in the Preceding Groups.—Seven cases could not be classified satisfactorily in the foregoing groups according to the presence or absence of congestive failure. Because of the unusual interest of this small group of patients with regard to the occurrence of low voltage, the seven case histories have been summarized.

Case 5.—F. M., a white woman, aged 44, was admitted to the hospital on Sept. 14, 1930, because of severe cardiac insufficiency due to rheumatic heart disease with stenosis and insufficiency of both the mitral and the aortic valves. An electrocardiogram taken on September 15 showed sinus rhythm, incomplete bundle branch block and many auricular premature beats. The waves were of normal amplitude. On September 19, a similar record was obtained. By September 25, the sinus rhythm had been replaced by auricular fibrillation. The voltage remained normal. A fourth record taken on September 29 was similar to the third. The patient's course during this period was one of steady clinical improvement. An electrocardiogram taken on October 6 showed that the auricular fibrillation and the incomplete bundle branch block were still present, but, in addition, low voltage was now present for the first time. Another record showed no change on October 14. At this time the patient had reached the peak of her improvement. Sinus rhythm reappeared in the electrocardiogram of October 20, although the block and low voltage persisted. About October 23 it was noted that the patient's condition was worse, and from that date her course was steadily downhill until she died, on November 15. Further electrocardiograms were taken on October 27 and on November 3. They were practically identical with the record of October 23. The low voltage persisted.

Comment: The preceding case is interesting because the low voltage, which was absent on admission during a serious cardiac break, appeared at the height of clinical improvement and antedated by over two weeks a turn for the worse in the patient's clinical condition which led to a fatal outcome.

Case 6.—L. S., a woman, aged 21, who had rheumatic heart disease, was admitted to the hospital markedly decompensated. On the next day, an electrocardiogram showed a rate of 120 beats per minute, auricular extrasystoles and a

shifting pacemaker. The voltage was normal. On her second day in the hospital, the heart rate became very rapid. An electrocardiogram disclosed that this was an auricular tachycardia. The rate was 200, and low voltage had appeared. A few hours after the record was taken the patient died.

Comment: In this case low voltage was not present when the patient was admitted with severe congestive failure, but developed a few hours before death, coincidently with the appearance of an ectopic auricular tachycardia.

CASE 7.—N. S., an Irish woman, aged 54, with diabetes mellitus and marked general arteriosclerosis, entered the hospital following a coronary thrombosis. Electrocardiograms taken on the second, sixteenth, twenty-seventh and thirty-third days in the hospital showed successive changes in the T waves thought to be characteristic of the sequence seen after a coronary occlusion. Low voltage was observed in each of these records, although cardiac insufficiency was not present. On her forty-first day in the hospital, a fifth electrocardiogram showed that the low voltage had disappeared. The patient was discharged four days later apparently in good condition. A few weeks later pneumonia developed and she was readmitted. At this time, she showed moderate cardiac insufficiency with edema of the ankles. Low voltage reappeared in the electrocardiogram. Only one record was secured during this admission.

Comment: In this patient low voltage appeared following a coronary accident but without demonstrable cardiac insufficiency. It disappeared coincidently with improvement in the patient's condition, and reappeared later when she developed cardiac insufficiency precipitated by pneumonia.

CASE 8.—I. A., a white man, aged 51, with arteriosclerotic heart disease, was admitted to the hospital severely decompensated on June 7, 1929; he was discharged on September 16. While in the hospital he showed slow but steady improvement, and on discharge his heart was considered well compensated. During this period, eleven electrocardiograms were taken. All records showed left axis deviation, inversion of T_1 and low voltage. In the follow-up clinic, where he was observed for three months after discharge, a similar record was obtained.

Comment: Low voltage was present in this case on admission, when the patient was severely decompensated. Although compensation was restored, the low voltage persisted and was again present in the follow-up clinic.

CASE 9.—S. S., a white woman, aged 42, was admitted to the hospital severely decompensated. She was found to have rheumatic heart disease with mitral stenosis and insufficiency and auricular fibrillation. Electrocardiograms taken on her first, second and third days in the hospital showed auricular fibrillation and right axis deviation. Low voltage was not present. The patient improved satisfactorily until the beginning of her second week in the hospital when pneumonia developed; she died six days later. During the course of the pneumonia, cardiac insufficiency again became manifest, and on the tenth day in the hospital a final electrocardiogram showed that low voltage had appeared.

Comment: Low voltage, which was absent during the congestive failure that was present on admission, appeared during a return of cardiac insufficiency due to a terminal pneumonia.

CASE 10.—J. J., a white man, aged 57, was admitted to the hospital the first time following thrombosis of a coronary artery. There was no evidence of cardiac insufficiency. In fact, at first the patient afforded a diagnostic problem, as all his pain was abdominal. An electrocardiogram showed an iso-electric T_1 and low voltage. Seven months later he was readmitted because of cardiac insufficiency. Two electrocardiograms taken during this admission each showed low voltage. A month later the patient was admitted for a third time because of recurrence of edema and dyspnea. Again an electrocardiogram showed low voltage.

Comment: In this case low voltage was present on the first admission in the absence of cardiac insufficiency. On two subsequent admissions with cardiac failure low voltage persisted.

CASE 11.—J. L., a man, aged 36, gave a history on admission to the hospital extremely suggestive of coronary thrombosis, despite his relatively youthful age. The pain and shock had been followed rapidly by cardiac insufficiency, with the result that at the time of admission he was severely decompensated. An electrocardiogram taken shortly after entry showed marked deformity of the Q-R-S group, but the waves were of normal amplitude. On his twelfth day in the hospital, he had a pulmonary embolus. On that day an electrocardiogram showed low voltage. Five days later the voltage was again normal and remained so until discharge after nearly three months.

Comment: Low voltage, which was absent when the patient was admitted with marked cardiac insufficiency, appeared temporarily following pulmonary infarction.

OCCURRENCE OF LOW VOLTAGE IN PATIENTS WITHOUT OBVIOUS HEART DISEASE

There were fifty-one patients whose electrocardiograms showed low voltage but who clinically did not present evidence of cardiac disturbance. It is not surprising that this series is smaller than the group with manifest organic heart disease, as more electrocardiograms are usually taken on patients with heart disease than on those without.

A diversity of pathologic conditions was present in the patients of this group. Eleven of the fifty-one patients had pneumonia, but in only one of them was there demonstrable fluid in the pleural cavity. There were eight cases of neoplasm, usually in the terminal stages. In two of the eight there was a pericardial or pleural effusion. There were six cases of hypothyroidism. Of these, three were definitely instances of myxedema. Rheumatic fever accounted for five cases. Low voltage usually occurred at the peak of an acute exacerbation. There were four cases of severe anemia, in two of which general anasarca was present.

These five conditions—pneumonia, neoplasm, hypothyroidism, rheumatic fever and severe anemia—account for thirty-four of the fifty-one cases (67 per cent).

The remaining seventeen cases may be disposed of briefly: polyserositis, three cases; pulmonary tuberculosis, three; bronchial asthma, two; polycythemia, one; chronic deforming arthritis, one; "gastro-enteritis," two; diabetic acidosis, one; cirrhosis of the liver with ascites, one; dermatitis medicamentosa, one; undiagnosed, one; fever of unknown origin, one.

On summarizing this group of fifty-one cases, it is found that in thirty-nine (76 per cent) there was no evidence of edema, ascites or pericardial or pleural effusion. The absence was often corroborated at autopsy. In the remaining twelve cases (24 per cent) an excess of fluid was present in one of the serous cavities or as edema.

It is, of course, impossible to say that all the patients in this "non-cardiac" group were free from organic heart disease. All that can be said is that this group was free from symptoms or physical signs pointing to cardiac disease and that, in those cases in which autopsies were performed, no evidence of pathologic changes in the heart could be found.

THE SIGNIFICANCE OF LOW VOLTAGE IN PATIENTS WITHOUT OBVIOUS HEART DISEASE

It would be foolhardy to attempt to draw conclusions from such a small series, especially in view of the fact that the cases must be subdivided according to diagnosis into even smaller groups.

The six patients with hypothyroidism were all living at the last report. In these cases it is probable that the appearance of low voltage was due to a local change in the skin itself and not to an altered cardiac function.

Two of the four patients with severe anemia had anasarca. These two patients were alive and in good condition one and a half and four years, respectively, after low voltage was detected in the electrocardiogram. The other two patients did not show even slight edema of the ankles, yet low voltage was present. These patients were alive after eight months and four years, respectively. Apparently, the appearance of the electrocardiographic abnormality was of no significance.

In contrast to the two preceding subgroups were the eight cases of neoplasm. The eight patients died, as might be expected from the nature of their disease. One patient survived for two and a half months after the electrocardiogram showed low voltage. The average duration of life for the group, however, was four weeks. Nothing of the Q-R-S group was present in the records of four of these patients, and auricular

fibrillation was observed once. In one patient a hydropericardium secondary to metastatic involvement of the pericardium was found at autopsy. A second case showed no edema or effusions and the heart was normal at autopsy.

The group with rheumatic fever is of some interest. All five patients were alive at the last report. In four cases low voltage was present on admission, at a time when the disease was most acute, and disappeared with the subsidence of symptoms and signs of activity. In three of these four there was also prolongation of the P-R interval, which disappeared with improvement in the patient's condition. The fifth patient had an essentially normal electrocardiogram at first, but low voltage developed during a flare-up of the rheumatic process. As in the other four cases, low voltage was again a transient anomaly. It is tempting to speculate that in these five patients with rheumatic fever the occurrence of low voltage was in some way connected with the exudative phenomena present during acute episodes of the disease process.

The seventeen miscellaneous cases considered together as one group are too few to analyze satisfactorily. Thirteen patients were living when last heard of. One patient with polyserositis died three years after discharge. The patient whose condition was undiagnosed died two weeks after the electrocardiogram was taken, and aside from necrosis of the liver nothing could be found at autopsy to account for death. The heart was normal. Two of the three patients with pulmonary tuberculosis died. In one of these death occurred in another hospital several months after transfer. In the other, death occurred on the same day that the electrocardiogram was taken. Death was the result of a miliary dissemination. No edema was present, nor was there an abnormal amount of free fluid in the serous cavities. The heart was normal.

In the foregoing forty cases it appears that the finding of low voltage in the electrocardiogram was not of much significance. Sometimes it was associated with edema, hydropericardium, ascites or pleural effusion. In other instances, as in the neoplasm group, it seemed to occur in a cachectic state, which may be assumed to have included the myocardium.

There remain to be considered the eleven patients with pneumonia. In ten of these patients there was no evidence of edema, empyema, pleural effusion or involvement of the pericardium. One patient had both empyema and purulent pericarditis and died with a terminal septicemia. It may be of significance that six (55 per cent) of the eleven patients died, which is a considerably higher mortality rate than that of patients with pneumonia as a group. Autopsies were performed on

three patients. Two of the cases showed no excess of free fluid in the pericardial or pleural cavities, and in both the heart was normal. In the third case, already alluded to, there were empyema and suppurative pericarditis. Although this series is small, it seems that the occurrence of low voltage in the electrocardiograms of patients with pneumonia may be of serious prognostic import.

THE SIGNIFICANCE OF LOW VOLTAGE IN PATIENTS WITH CARDIAC DISEASE

In an attempt to attain a closer approximation of the significance of low voltage appearing in the electrocardiograms of patients with heart disease a "control" group of patients with heart disease was selected for purposes of comparison with the group with low voltage. One hundred patients with heart disease but without low voltage in the electrocardiograms were chosen as controls. The only basis for selection was a temporal one. For example, ten patients (9 per cent) of the low voltage group entered the hospital in 1925. To make the control series comparable, 9 per cent of the patients for this series were accordingly selected from the files for 1925, and so on for each of the ten years included in this survey.

TABLE 1.—*Comparison of the Control Group with the Low Voltage Group*

Etiology	Control Group	Low Voltage Group
Arteriosclerotic	67%	67% (76 cases)
Rheumatic	27%	25% (28 cases)
Syphilitic	6%	6% (7 cases)
Miscellaneous	0%	2% (2 cases)
	100%	100%
Average age	50 years	53 years
Presence of cardiac insufficiency (congestive)	59%	56%
Presence of other electrocardiographic abnormalities	73%	80% (90 cases)

That the two groups are comparable in addition to the time relationships may be seen from table 1.

Comparison of Mortality Rates.—For the Two Entire Groups: No follow-up data were obtained for twenty-three patients in the group of 113 with low voltage in the electrocardiogram. Of the remaining ninety patients, fifty (56 per cent) were known to be dead within an average period of ninety-two days, while forty patients (44 per cent) were known to be alive after an average of thirteen and one-half months. In the control group of a hundred cases it was possible to follow ninety-eight. Of the ninety-eight patients for whom some follow-up reports were obtained, sixty-nine (70 per cent) were alive after an average of twenty months, while twenty-nine (30 per cent) were dead after an average of one year and nine months.

The results may be summarized as follows:

Low voltage group (90 cases)	Alive, 44% in 13½ months Dead, 56% in 3 months
Control group (98 cases)	Alive, 70% in 20 months Dead, 30% in 21 months

By Age Groups: Ninety-eight cases in the control series were arranged by decades and compared with the ninety cases showing low

TABLE 2.—*Comparison of Mortality by Age Groups*

			Living			Dead		
Decade	Group	Total Cases	Number	Percentage	Average Duration of Observation in Days	Number	Percentage	Average Duration of Observation in Days
0-9 yrs.	Low voltage	1	0	..	....	1	100	60
	Control	0	..	..	....	..	....	....
10-19 yrs.	Low voltage	3	0	..	....	3	100	7
	Control	14	7	50	741	7	50	720
20-29 yrs.	Low voltage	1	0	..	....	1	100	1
	Control	4	3	75	803	1	25	30
30-39 yrs.	Low voltage	11	6	55	310	5	45	195
	Control	7	5	71	350	2	29	820
40-49 yrs.	Low voltage	21	10	48	450	11	52	67
	Control	23	19	83	637	4	17	818
50-59 yrs.	Low voltage	29	16	55	355	13	45	174
	Control	29	19	66	549	10	34	398
60-69 yrs.	Low voltage	17	6	35	675	11	65	60
	Control	15	13	87	615	2	13	143
70-79 yrs.	Low voltage	7	2	29	203	5	71	49
	Control	6	3	50	607	3	50	1,388

TABLE 3.—*Comparison of the Mortality According to Etiologic Groups*

Etiology	Group	Total Cases	No Follow-Up	Cases Followed	Number Living	Percentage Alive	Average Duration of Observation in Days	Number Dead	Percentage Dead	Average Duration of Observation in Days
Arteriosclerotic	Low voltage	76	16	60	32	53	410	28	47	119
	Control	67	2	65	47	72	532	18	28	596
Rheumatic	Low voltage	28	6	22	6	27	485	16	73	83
	Control	27	0	27	18	67	898	9	33	605
Syphilitic	Low voltage	7	1	6	1	17	210	5	83	46
	Control	6	0	6	4	67	60	2	33	76
Miscellaneous	Low voltage	2	0	2	1	50	240	1	50	60
	Control	0	..	..	..	..	....	..	..	....

voltage. The results may be seen in table 2. In this table the term "average duration of observation" refers to the average duration of the period of observation in the follow-up clinic in the group of living patients or the duration of observation before death in those cases in which the patients were known to have died.

It will be noted that the mortality of the patients who showed low voltage in their electrocardiograms was greater in all decades than the controls, and that the period of observation before death was shorter

in each case. Among the patients who were still alive, the difference in duration of the periods of observation for the two groups was less striking, but in only one instance (the decade from 60 to 69 years) was this period greater in the low voltage group than in the controls.

By Etiologic Groups: The mortality of the patients showing low voltage was greater than that of the controls in each of the three main groups of heart disease, as seen in table 3. The difference was least marked in patients with arteriosclerotic heart disease. It was striking, however, in both the rheumatic and the syphilitic group, in which the mortality in the low voltage series was 73 and 83 per cent, respectively, as compared to 33 per cent in each instance in the control group.

TABLE 4.—*Mortality in Groups With and Without Congestive Failure*

Congestive Failure	Group	Total Cases	No Follow-Up	Cases Followed	Number Living	Percentage Alive	Average Duration of Observation in Days	Number Dead	Percentage Dead	Average Duration of Observation in Days
Present	Low voltage	63	11	52	22	42	452	30	58	121
	Control.....	55	0	55	34	62	620	21	38	477
Absent	Low voltage	43	12	31	15	48	406	16	52	80
	Control.....	45	2	43	35	81	584	8	19	828

TABLE 5.—*Comparison of the Mortality in Groups With and Without Other Electrocardiographic Abnormalities*

Electrocardiographic Abnormalities	Group	Total Cases	No Follow-Up	Cases Followed	Number Living	Percentage Alive	Average Duration of Observation in Days	Number Dead	Percentage Dead	Average Duration of Observation in Days
Present	Low voltage	90	16	74	36	49	427	38	51	129
	Control.....	73	1	72	48	67	570	24	33	413
Absent	Low voltage	23	7	16	3	19	160	13	81	49
	Control.....	27	1	26	24	92	561	2	8	180

According to the Presence or Absence of Congestive Failure: In the group of patients with low voltage in the electrocardiogram it will be recalled that sixty-three had edema, ascites, hydrothorax or pericardial effusion, while in forty-three cases there was no evidence of abnormal accumulation of fluid. In addition there were seven cases that could not be put successfully into either group. It becomes apparent from a study of table 4 that the mortality is greater both in the presence or in the absence of congestive failure when low voltage is present in the electrocardiogram than in the control group without low voltage.

According to the Presence or Absence of Other Electrocardiographic Abnormalities: In 80 per cent of the group of cases showing low voltage in the electrocardiogram other abnormalities were present, such as auricular fibrillation, inversion of T_1 or T_2, block (both auriculo-

ventricular and intraventricular) or marked deformity of the Q-R-S group. Similar abnormalities were present in 73 per cent of the control group. In table 5 the comparisons are summarized. Regardless of the presence or absence of other electrocardiographic abnormalities, the mortality is greater in the low voltage group than in the control series. A point of interest is the greater mortality in the cases with low voltage in which low voltage was the only significant change in the record. Perhaps this is a statistical artefact, but, in this small series at least, it would appear that the prognosis is grave when low voltage is an isolated finding.

SUMMARY AND CONCLUSIONS

1. The records of 164 patients who have shown low voltage in their electrocardiograms have been analyzed.

2. One hundred and thirteen patients had manifest heart disease. In the remaining fifty-one cases without apparent cardiac involvement, a variety of diseases was present.

3. In the group with heart disease, low voltage appeared to be related to the presence of congestive failure in sixty-three cases, but congestive failure was absent in forty-three cases, and seven cases could not be classified.

4. In the group of patients without heart disease, an abnormal accumulation of fluid was present in thirty-nine cases and absent in twelve cases.

5. The significance of low voltage in patients without obvious heart disease is not clear. It is suggested that its occurrence in pneumonia is of serious prognostic import.

6. In patients with heart disease low voltage appears to be of considerable prognostic significance. In comparison with a control group the mortality was greater within a shorter period of observation in the low voltage group. This was true regardless of age, type of heart disease, presence or absence of congestive failure and presence or absence of other electrocardiographic abnormalities.

TREATMENT OF ADDISON'S DISEASE WITH CORTIN (HARTMAN)

REPORT OF FOUR CASES

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That substitution treatment of Addison's disease is not yet fully developed at first thought seems surprising. It is certainly not Addison's fault. In 1855 he not only described the disease but demonstrated its cause. This was seventeen years before Sir William Gull, his colleague at Guy's Hospital, merely described myxedema, and twenty-seven years before Kocher and Reverdin showed that myxedema is due to lack of thyroid tissue. In spite of this later start, myxedema is now easily treated with replacement therapy, while Addison's disease remains a problem. The knowledge concerning replacement therapy in other later described endocrine deficiencies, such as diabetes and parathyroid tetany, has likewise passed far beyond that in Addison's disease.

Just as progress of knowledge in Addison's disease has been slow, so is evaluation of treatment difficult, and for the same reason. Science, in the final analysis, depends on measurements. No measuring stick has been found for insufficiency of the suprarenal cortex. The worker in this field looks with envy at the determinations of blood calcium, blood sugar and basal metabolism, which serve as measuring sticks in other fields of endocrinology. The experimenter in insufficiency of the suprarenal cortex has had to rely almost entirely on the cumbersome measuring stick furnished by prevention of death in adrenalectomized animals. Indeed the one physiologic fact that can be stated with certainty regarding the hormone of the suprarenal cortex, which was first demonstrated in 1856 by Brown-Séquard (a former member of the staff of this hospital, who was appointed to the Board of Consultants of the Massachusetts General Hospital in 1864), is that it is necessary for life.

From the medical services of the Massachusetts General Hospital.

In spite of this handicap, extracts have been prepared that will prolong life in adrenalectomized animals,[1] and there are now extracts that will keep adrenalectomized animals alive indefinitely.[2] These extracts have been found to be of value in the treatment of patients with Addison's disease.[3] This paper deals with the treatment of four patients with Addison's disease by means of Hartman's extract, cortin.

Before presenting the data, we wish to point out that clinical evidence is always largely circumstantial. This is especially true in regard to Addison's disease, because of the lack of a delicate measuring stick and the tendency to spontaneous remissions. The evidence that we shall present is admittedly largely circumstantial. Such evidence, if based on enough observations, should constitute proof. We believe, in case 4, moreover, that we have evidence that is more than circumstantial.

The preparation of cortin used in all of our cases was supplied by Dr. Frank A. Hartman and shipped to Boston from Buffalo. In this paper the dosage is expressed in cubic centimeters. Each cubic centimeter represents the extract of 50 Gm. of adrenal cortex. The usual daily dosage was from 16 to 20 cc. administered subcutaneously in four divided doses.

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REPORT OF CASES

CASE 1.—*A 30 year old white married man, with active pulmonary tuberculosis, with extreme weakness and generalized pigmentation of six months' duration and with low blood pressure, showed marked symptomatic improvement when cortin was given in conjunction with fluids and dextrose by intravenous injection. He died seven days after treatment was discontinued.*

History.—Albert D., a 30 year old white married man, entered the hospital on March 31, 1931, complaining of weakness and epigastric pain of one year's duration, and was discharged on May 24, 1931. He died on May 31, 1931.

One year before admission epigastric pain and nausea had developed. The pain was dull and radiated both to the right and to the left. At about the same time the patient began to notice weakness, fatigability, somnolence, dizziness and pigmentation of the skin. Five months after the onset of the illness he was forced to stop work on account of weakness. The pigmentation continued to increase, as did other symptoms. He lost 17 pounds (7.7 Kg.) in weight.

The patient's past history revealed that he had had pleurisy for two weeks at the age of 18.

Physical Examination.—Examination showed a young man of medium stature with evidence of recent loss of weight. There was marked pigmentation of the skin and the buccal mucous membrane. The lungs were clear at the time of admission. The blood pressure was 92 systolic and 70 diastolic.

The results of laboratory tests were as follows: The Hinton test [4] was negative. The urine, red blood cell count, hemoglobin, white blood cell count and smear were within normal limits. The stool was normal. The sputum was positive for tubercle bacilli. The basal metabolic rate was minus 2. The blood sugar was 121 mg. per hundred cubic centimeters; the blood nonprotein nitrogen was 44 mg., and the blood cholesterol, 104 mg. The electrocardiogram showed slight right axis deviation. Roentgen examination of the chest showed coarse mottled dulness involving both apexes and the first interspaces. No roentgenographic evidence of calcification of the suprarenals was found.

Course of Illness.—After seven days of treatment, with the administration of a total of 98 cc. of cortin subcutaneously and 30 cc. of cortin intravenously and fluids in five intravenous injections of from 200 to 450 cc. each, the patient showed the following improvement: (1) disappearance of nausea and vomiting, (2) restoration of fair appetite and (3) increase of strength.

After eight more days of treatment, with a total of 152 cc. more of cortin administered subcutaneously, the patient's condition was remarkably good in every respect and he was eating with relish three meals daily. He continued to do well for twenty days following the institution of treatment. He then began to lose strength, and on the thirty-seventh day of treatment nausea and vomiting began again. This was temporarily controlled by an intravenous injection of 600 cc. of 10 per cent dextrose. The temperature, which at first had tended to be subnormal, rose to febrile levels. Many râles appeared over both pulmonary fields. Roentgen examination of the chest showed extension of the pulmonary process. It was decided that the patient would die of pulmonary tuberculosis even if the Addison's disease were controlled. A massive dose of cortin was given which arrested the nausea and vomiting. Treatment with cortin was then stopped, and the situation was explained to the family. The patient was taken home. He lived only one week after substitution therapy was discontinued. The patient lost 16 pounds (7.3 Kg.) during his fifty-five days in the hospital. Treatment was without effect

4. A serologic test for syphilis.

on the nonprotein nitrogen of the blood, which varied between 33 and 44 mg. per hundred cubic centimeters, or on the blood sugar, which varied between 121 and 144 mg. per hundred cubic centimeters. The blood cholesterol three days before discharge had sunk to 44 mg. per hundred cubic centimeters. The massive dose of cortin was given on that day, and on the following two days the cholesterol content was 83 and 89 mg., respectively.

Comment.—The evidence of the efficacy of the substitution treatment in this case rests on the disappearance of nausea and vomiting and the restitution of appetite and euphoria with the institution of treatment and on the shortness of the period of survival following the cessation of treatment. The evidence remains circumstantial, because other forms of treatment, the intravenous injection of dextrose especially, were used together with cortin.

CASE 2.—*A widow, aged 62, with recent onset of weakness, slight pigmentation and mild hypotension and with evidence of quiescent pulmonary tuberculosis, showed symptomatic improvement when the administration of cortin was added to other forms of treatment. Observations made during a nine day period of withdrawal of cortin are compared with similar observations during fore-periods and after-periods of administration of cortin.*

History.—Mrs. A. D. W., a widow, aged 62, was admitted to the New England Baptist Hospital, complaining of weakness, in March, 1931, where the diagnosis of Addison's disease was made by Dr. Albert Hornor. She was discharged on May 12, 1931, and was studied at the Massachusetts General Hospital in July, 1931.

Weakness and fatigability developed in January, 1931, four months prior to the institution of treatment. In April, 1931, nausea, vomiting, increase in pigmentation and low blood pressure appeared while the patient was under observation at the Baptist Hospital. Two years prior to the onset of these symptoms diabetes had suddenly developed. Concomitant with the onset of the symptoms of Addison's disease, the patient's tolerance for carbohydrate had risen so that she was now able to eat candy and other rich carbohydrate foods without the occurrence of glycosuria.

The past history revealed a mild chronic diarrhea of nineteen years' duration, ending in 1930. There had been pneumonia, followed by eight months of convalescence, in 1893, and hemoptysis on four occasions, from 1910 to 1920. Operations included hemorrhoidectomy in 1903 and tonsillectomy in 1927. Menstruation had always been scanty. The menopause had occurred at the age of 45. Before the onset of diabetes the patient weighed 152 pounds (68.9 Kg.), and afterward she weighed 139 pounds (63 Kg.). At the onset of the weakness, in January, 1931, she weighed 128 pounds (58.1 Kg.) and seven months later, 110 pounds (49.9 Kg.).

Physical Examination.—Examination on July 7, 1931, showed a well developed but poorly nourished woman. There were patchy pigmentation of the skin and slight purplish pigmentation of the tongue. There was enlargement of the left submaxillary glands, which were probably tuberculous. The blood pressure varied between 74 and 155 systolic and 55 and 100 diastolic during the period of observation. Râles were recorded at times at the apexes of both lungs, but a diagnosis of active pulmonary tuberculosis was not made. There were hypertrophic changes in the finger joints.

Laboratory tests showed: The urine was normal. The red blood cell count was 3,780,000; hemoglobin (Sahli), 77 per cent; the white blood cell count, 10,650, and the blood smear normal. The stool was normal. Roentgen examination showed hypertrophic changes in the joints, two calcified glands near the crest of the right ilium, diffuse mottled dulness at the apexes of both lungs and a small round area of calcification near the upper pole of the right kidney, thought to be a calcified gland rather than a calcification of the right suprarenal. The electrocardiogram showed low T waves in all leads; it was not affected by the administration of cortin.

Course of Illness.—Following an intravenous injection of gallbladder dye at the New England Baptist Hospital on April 10, marked weakness, nausea and vomiting developed. The patient could take no food by mouth, and she steadily lost in strength. Thirteen days after the onset of these gastro-intestinal symptoms, a patch of brown pigment appeared on the left side of the nose, and there was an increase in the already slight brownish pigmentation of the face, hands and legs. The patient continued to lose ground in spite of daily intravenous injections of 1,500 cc. of physiologic solution of sodium chloride reinforced with 50 Gm. of dextrose. These injections were commenced on April 12, two days after the onset of acute symptoms. The blood pressure dropped steadily from 120 systolic and 80 diastolic to 90 systolic and 60 diastolic, and the diagnosis was clear.

Twenty-seven days following the onset of nausea and vomiting the administration of cortin was begun. Four days later the patient began to eat, and her strength improved enough to allow her to sit up. Nausea and vomiting disappeared, but recurred on several occasions when the administration of cortin was stopped or the dosage was much lowered. Thus, on one occasion injections of cortin were replaced by injections of solution of sodium chloride for two days without the patient's knowledge; on the third day she was "weepy," and nausea and vomiting had recurred. These symptoms were promptly relieved by resumption of the administration of cortin. The degree of pigmentation was not definitely altered. After thirty-six days of treatment with cortin, the patient was discharged to her home, where she continued to receive cortin and to do well.

In July, 1931, the patient entered the ward for special research of the Massachusetts General Hospital for detailed studies. The plan was to make careful observations during a fore-period of administration of cortin, then during an experimental period with no cortin, and finally during an after-period with cortin. The data are given in table 1. During the period of withdrawal of cortin symptoms of acute insufficiency failed to develop, but the patient's appetite and euphoria were diminished, and she became generally weaker. The blood pressure fell, and rose again when treatment was resumed. The standing systolic pressure dropped from an average of 116 to an average of 87 mm. of mercury for the last five days of the period in which no cortin was given. By the sixth day after the reinstitution of treatment the systolic pressure had risen only slightly, to 94 mm. of mercury, but during the following forty-three days it continued to rise and reached an average value of 130 mm. of mercury. Similarly the standing pulse pressure decreased from the preliminary average figure of 31 to 18, and with treatment again rose to 22 and later to 29 mm. of mercury. The weight dropped from 49.4 to 48.5 Kg. and rose again to 49.4 Kg. The caloric intake dropped from 1,818 calories daily to 1,670 calories, but continued to fall during the five days when the patient was under observation in the hospital after the reinstitution of treatment. Later, on September 1 and 2, 145 cc. of cortin was given in addition to the usual 20 cc. daily. On September 3, there was the most amazing improvement, chiefly in appetite and in spirits, and for fifteen days thereafter the appetite was voracious for three hearty meals daily. The determinations in the fasting blood are interest-

TABLE 1.—*Data for Case 2 Showing Effect of Withdrawal of Cortin on Certain Variables*

Date	Cortin Given, Cc.	Clinical Condition	Caloric Intake, Calories	Blood Pressure Systolic		Basal Metabolic Rate	Blood Plasma						Urine					Weight, Kg.
				Reclining	Standing		Non-protein Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Lactic Acid, Mg. per 100 Cc.	Chlorides, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Creatine, Gm. per 24 Hours	Creatinine, Gm. per 24 Hours	Volume, Cc. per 24 Hours	Fluid Intake, Cc. per 24 Hours	Ergograph, Kg. Meters	
July 7	20	Good	.....	128	142	— 2	26	1.4	86	7.46	...	195	.....	.....	.....	.....	1.96	49.2
8	20	Good	1,800	122	120	—10	..	...	...	....	...	...	0.049	0.817	1,860	1,260	2.36	49.1
9	20	Good	1,802	117	105	—10	35	1.5	104	....	...	190	0.057	0.573	1,260	1,620	2.86	49.8
10	20	Good	1,802	103	107	— 5	29	1.5	95	....	604	189	0.105	0.863	1,860	1,740	2.08	49.7
11	20	Good	1,871	112	108	— 2	..	...	...	.....	...	...	0.108	0.882	1,980	1,800	2.46	49.0
12	..	Good	1,871	110	106	.....	..	...	...	.....	...	...	0.106	0.705	1,980	2,160	3.10	49.0
13	..	Good	1,871	103	98	— 8	26	1.5	108	.....	601	189	0.265	1.014	2,700	2,220	3.46	49.2
14	..	Good	1,833	101	100	— 6	..	...	...	.....	...	...	0.094	0.763	1,770	1,650	3.26	48.6
15	..	Weakness	1,736	107	81	+ 2	35	1.5	112	.....	603	188	0.151	0.819	1,830	1,980	2.80	48.7
16	..	Fatigue	1,756	108	93	— 3	..	...	...	4.82	...	...	0.121	0.759	2,040	1,860	3.24	48.7
17	..	Nausea	1,811	100	90	— 2	30	1.5	124	7.76	594	184	0.139	0.792	1,800	1,950	2.60	48.3
18	..	Dizziness	1,658	110	93	— 3	..	...	...	....	...	...	0.126	0.712	1,440	1,980	3.66	48.3
19	..	Dizziness	1,505	100	98	.....	..	...	...	....	...	...	0.137	0.823	1,800	1,980	2.78	48.7
20	..	Dizziness	1,559	102	73	— 7	35	1.5	133	....	597	189	0.190	0.801	1,800	1,980	2.94	48.5
21	66	Hiccoughs	1,474	98	89	— 3	35	1.5	136	....	562	188	0.241	0.650	1,340	2,040	3.54	48.5
22	81	.....	1,663	105	83	—17	..	...	...	....	...	...	0.160	0.658	1,380	2,040	2.60	48.4
23	60	Euphoria	1,556	108	99	—11	30	1.5	109	....	584	193	.....	.....	1,340	2,040	2.82	49.4
24	60	Very well	1,620	108	91	— 9	..	...	...	....	...	...	0.273	0.689	1,170	2,040	2.86	49.7
25	5	Very well	1,495	110	93	— 3	29	1.5	90	....	591	188	0.142	0.629	1,860	2,040	3.96	49.2
26	..	Very well	.....	111	97	....	..	...	...	....	...	...	0.186	0.708	1,470	2,040	3.50	49.4
Aug. 18	20	Poor	.....	116	100	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
19	20	.....	.....	124	92	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
20	20	.....	.....	135	110	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
21	20	Excellent	.....	135	120	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
22	20	.....	.....	136	115	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
23	20	.....	.....	156	116	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
25	20	Very well	.....	141	120	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
26	20	.....	.....	134	140	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
27	20	Vomits	.....	150	124	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
29	20	Nausea	.....	138	80	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
31	20	Nausea	.....	133	82	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
Sept. 1	132	Weakness, nausea	.....	117	72	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
2	53	Better	.....	125	90	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
3	20	Excellent	.....	120	75	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
5	20	Excellent	.....	110	80	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
8	20	Excellent	.....	122	112	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
10	20	Excellent	.....	92	70	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
13	20	Excellent	.....	124	90	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
18	10	Excellent	.....	138	105	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
19	10	Fair	.....	130	92	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
20	20	Fair	.....	124	90	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....
23	20	Fair	.....	132	122	....	..	...	...	....	...	...	.....	.....	.....	.....	.....	.....

ing only in that they show practically no changes. The blood sugar rose slightly during the period with no cortin and fell the same amount with the reinstitution of treatment. The nonprotein nitrogen, creatinine, cholesterol and chlorides of the blood were not affected. Likewise the basal metabolic rate and the urinary excretion of creatine and creatinine were unaltered. The ergograph tracings belied the clinical impression and showed a steady improvement. Thus the work done rose in the three successive periods from 2.3 to 3.2 to 3.4 kilogrammeters. This rise we attribute to practice rather than to improvement.

At the time of writing, eight months after the institution of treatment, the patient is still receiving cortin. She goes driving, entertains guests at tea and, on the whole, finds life pleasurable.

Comment.—The evidence of the efficacy of substitution treatment in this case rests on the disappearance of nausea and vomiting when cortin was added to other forms of treatment that the patient was already receiving, on the many months without a relapse when she was receiving cortin daily, on the recurrence of symptoms when cortin was withdrawn and on the decrease of blood pressure when cortin was omitted.

CASE 3.—*In a 17 year old school girl of Italian descent, with arrested pulmonary tuberculosis and calcification in the suprarenal gland on one side revealed by roentgen examination, with a history of weakness for four years, acute suprarenal insufficiency developed. She was rescued from this complication by means of treatment that included cortin. Observations made during a four month period of treatment with cortin are compared with similar observations after the withdrawal of cortin.*

History.—Della D. was admitted to the Massachusetts General Hospital on April 6, 1931, complaining of weakness and pigmentation, and discharged to Johns Hopkins Hospital on Oct. 24, 1931.

Increasing pigmentation was noted four years before admission and had continued ever since. At the time of admission the patient was as dark as an East Indian. For the past five years she had been undernourished, and for three years she had been under the supervision of the board of health. Marked weakness and fatigue had been noted for only one year. A slightly productive cough developed shortly before her entrance to the hospital.

The mother had been "cured" of tuberculosis ten years before. The patient's past history included diphtheria and pertussis. The patient was treated, five years before admission, at the Reading Sanatorium for tuberculosis of the hilus.

Physical Examination.—Examination showed undernourishment, marked pigmentation of the entire skin and patches of pigmentation on the tongue and the buccal mucous membranes. The blood pressure was 98 systolic and 65 diastolic while the patient was lying down and 80 systolic and 60 diastolic while standing.

Laboratory studies showed: The Hinton test was negative. The urine, red blood cell count, white blood cell count and smear were within normal limits. The basal metabolic rate was minus 12 and minus 18. The sputum was negative for tuberculosis. Roentgen examination showed definite calcification in the region of the left suprarenal gland, increase in width and density of the pulmonary roots and mottling in the first and second left interspaces.

Course of Illness.—Eight days after admission the patient suddenly lost her appetite, became nauseated and vomited. She became critically ill. Her temperature first sank below normal and then rose to 103 F. The pulse rate rose to 120,

and the blood pressure dropped from 15 to 20 points. All forms of therapy were administered, including moderate doses of cortin and intravenous injections of dextrose, and the patient recovered. The blood pressure, however, remained low. Two weeks later, in spite of a daily dose of 16 cc. of cortin, a subnormal temperature (96 F. by mouth) developed, which was again followed by a high temperature (101.6 F.) and collapse. Again intravenous injection of dextrose was resorted to, and large doses of cortin were administered. Again the patient made a miraculous recovery. Cortin, from 20 to 24 cc. daily, was continued for three months without further mishap. The systolic pressure vacillated around 80 mm. of mercury. The patient lost 2.3 Kg. in weight. The pigmentation remained unchanged. She was able to walk around the premises. After these three months of treatment, cortin was omitted in order to study the effect of withdrawal on certain variable factors. During the next two and a half months the patient received no cortin and did well. She gained 5.3 Kg. The most significant change was a definite increase in the tendency to subnormal temperatures. During this period the basal metabolism varied from minus 2 to minus 28 (it was from minus 16 to minus 24 during the treatment with cortin); the fasting blood sugar varied from 66 to 84 mg. per hundred cubic centimeters (it was 67 and 81 mg. during treatment with cortin); the blood nonprotein nitrogen varied from 20 to 25 mg. per hundred cubic centimeters (it was 24 and 26 mg. during treatment with cortin), and the ergographic records remained about the same. The blood cholesterol requires special comment. It was 127 and 124 mg. per hundred cubic centimeters during treatment with cortin. The level on the whole was not affected by withdrawal of cortin. Thus, two weeks after withdrawal the blood cholesterol was 128 mg. About three weeks after withdrawal, however, the level was found one morning to be 367 mg. The serum at this time was lipemic. Two days later the level was 138 mg. No explanation for this sudden rise was found.

Comment.—The evidence of the efficacy of treatment in this patient rests on her rescue twice from a state of acute suprarenal insufficiency concomitant with treatment with cortin. The evidence remains circumstantial again, because other forms of therapy for collapse were employed. The fact that both acute episodes were preceded by subnormal temperatures is interesting, as adrenalectomized animals are very susceptible to low temperatures. The lessened tendency to subnormal temperature during the administration of cortin is also noteworthy and is again in agreement with the results of animal experimentation.

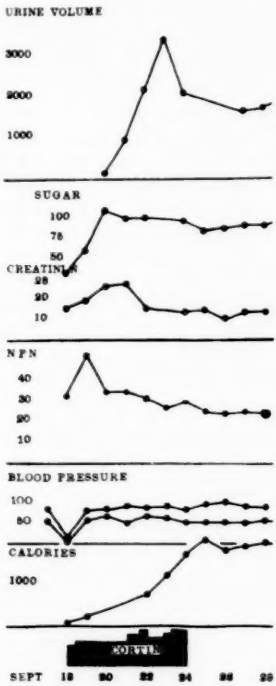
CASE 4.—*A 36 year old housewife with asthenia and hypotension of several years' duration and pigmentation of several months' duration, with no evidence of tuberculosis and a negative tuberculin test, went into a state of acute suprarenal insufficiency. By means of cortin alone she was revived from a moribund condition.*

History.—Rose M. C., a 36 year old married woman, entered the Massachusetts General Hospital for the fourth time on Aug. 19, 1931, complaining of weakness, and was discharged to the Johns Hopkins Hospital on Oct. 28, 1931.

Weakness had been present for three and one-half years at the time of her first admission in 1927. At that time the tendency to remissions of the condition was commented on, and this has characterized the later history. An erroneous diagnosis of myasthenia gravis was made on the first admission, because muscles

supplied by cranial nerves were especially involved. This aspect of the illness was not present on later entries. One month before the last admission weakness became so great that the patient was confined to an existence in bed and chair. Pigmentation, though described as "diffuse brownish" at her second admission in 1927, was minimal until one month before the fourth admission. Nausea had been present at varying intervals. It had been especially marked during the month before the last admission, during which the patient had lost 8 pounds (3.6 Kg.).

Until the fourth admission, attention had been focused on a condition probably unrelated to Addison's disease, namely, a mediastinal tumor. This tumor was situated in the region of the left auricle, was smooth in outline, had not changed



Graphic representation of the effect of cortin on certain variables in case 4.

in size during the four years of observation and was not affected by roentgen irradiation. By bronchoscopy it was shown to be pressing on the left descending bronchus. To this growth were attributed the recurring attacks of bronchitis and the signs in the lower lobe of the left lung. The patient had a productive cough on admission.

At the age of 10 years the patient had had a cervical abscess, which was opened and drained. She had had nocturia "all her life." The history of catamenia was normal.

Physical Examination.—Examination showed a poorly nourished woman with diffuse, marked, brownish pigmentation, including patches of pigmentation on the tongue. The heart was normal, except for an enlarged supracardiac dulness (per-

haps caused by the tumor). The blood pressure was 90 systolic and 60 diastolic (it had been 95 systolic and 65 diastolic on her first admission). The chest showed signs at the base of the left lung consistent with localized chronic pulmonary infection due to bronchial compression.

Laboratory studies showed: The Hinton test was negative. The urine, red blood cell count, white blood cell count and blood smear showed nothing remarkable. Roentgen examination of the suprarenals revealed no calcification. The tuberculin tests with a dilution of 1:10,000 (human and bovine) were negative at forty-eight hours. Gastric analysis showed no free hydrochloric acid while fasting or after the injection of ergamin.

Course of Illness.—After one month in the hospital with nonspecific treatment, the patient had a sudden severe turn for the worse. On September 17, nausea and vomiting, tachycardia and circulatory collapse developed. By the following afternoon the patient had sunk into a state of extreme suprarenal insufficiency. The blood pressure was 40 systolic. The pulse rate was rapid and could not be determined at the wrist. The arms and legs, in spite of a rectal temperature of 99.2 F., were icy cold, as in dying persons. The patient was oliguric and dehydrated. The consensus was that she would die within a few hours. The sensorium was relatively clear, considering the condition. The situation seemed so hopeless that the question as to whether the limited supply of cortin should or should not be used was raised. However, it was decided to make use of large doses of cortin with the addition of none of the usual adjuncts to treatment, such as fluids given intravenously in the form of solutions of dextrose or sodium chloride.

The effect of treatment was almost miraculous. The details are shown in table 2 and the chart. Six hours after the first injection the patient was able to drink orange juice and was beginning to move around in bed. The heart rate had slowed from 135 to 120. The pulse could be felt at the wrist at intervals. The extremities were warmer. Within fifteen hours the patient became almost euphoric, could take fluids easily by mouth and had a pulse rate of 106. The blood pressure could be obtained again, and was 70 systolic and 52 diastolic. Improvement continued. By the fourth day a craving for saltine crackers developed (table 2, on chlorides), and by the sixth day the patient's appetite had become voracious. Double vision, which had been present, disappeared on the fifth day. Headaches, which the patient had had daily for a year, disappeared for ten days following treatment.

The changes in the chemical composition of the blood resulting from treatment with cortin are shown in the chart. The blood sugar rose from 35 to 111 mg. per hundred cubic centimeters in forty-eight hours. As the urinary secretion rose, the high nonprotein nitrogen and creatinine levels of the blood fell.

Comment.—The insidious onset, the negative tuberculin tests and the absence of apical lesions suggest that this patient was suffering from the type of Addison's disease with atrophy of the suprarenal cortex. We believe that the evidence of the efficacy of treatment in this patient is more than circumstantial. Except for cortin, all forms of treatment known to be of value in acute collapse from suprarenal insufficiency were withheld. With cortin alone the patient recovered. Insulin in diabetic coma is no more convincing than cortin was in this case. Having been rescued from acute collapse, the patient maintained the good condition induced without further treatment with cortin, thus showing that the suprarenals had power to recover. This observation has been reported by others.[3g]

TABLE 2.—*Data for Case 4*

Date	Cortin Given, Cc.	Clinical Condition	Caloric Intake, Calories	Blood Pressure		Pulse		Temperature, Degrees F.	Blood Plasma					Urine			Ergograph, Kg. Meters	Weight, Kg.
				Systolic	Diastolic	Reclining	Standing		Non-protein Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Chlorides, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Creatine, Gm. per 24 Hours	Creatinine, Gm. per 24 Hours	Volume, Cc. per 24 Hours		
Sept. 17	..	Relapse	.....	90	60	117	...	97.3	..	...	...	...	...	.....	.....	.....	....	....
18	28	Moribund	50	20	9	125	...	98.6	33	1.6	35	530	188	.....	.....	.....	....	....
19	30	Out of danger	200	84	60	117	...	98.8	53	2.0	66	...	156	.....	.....	.....	....	....
20	30	Improving	.....	87	70	109	...	99.5	35	2.7	111	486	156	0.126	0.143	140	....	....
21	42	No nausea	.....	95	52.5	106	...	99.5	35	2.8	102	477	179	0.576	0.556	940	....	....
22	36	Good appetite	770	90	70	98	...	99.8	32	1.6	103	485	164	0.462	0.759	2,800	....	....
23	44	Excellent	1,230	95	66	88	...	99.4	27	...	...	...	...	0.246	0.743	3,420	....	....
24	..	Voracious appetite	1,762	89	55	90	...	99.8	30	1.4	98	500	152	0.201	0.554	2,014	0.5	....
		Stronger	2,115	100	55	89	...	99.5	25	1.5	86	550	150	.....	.....	.....	0.55	....
25	..	Excellent	1,850	104	56	92	...	99.5	24	1.1	89	...	...	.....	.....	.....	0.70	45.4
26	..	Excellent	1,942	94	52	90	...	99.5	25	1.4	92	549	142	0.056	0.464	1,635	0.80	....
27	..	Excellent	2,025	98	58	96	...	98.8	24	1.4	92	546	155	0.162	0.475	1,745	0.80	....
28	..	Headache	2,000	95	56	105	...	99	24	1.4	100	552	150	0.120	0.756	1,900	0.80	....
29	..	Good	2,385	91	51	92	...	99	..	...	...	...	...	0.106	0.653	1,765	1.00	....
30	..	.....	2,550	91	59	10	...	99	..	...	...	...	...	.....	.....	.....	1.05	....
Oct. 1	..	.....	1,475	98	65	95	...	99	30	1.4	84	510	169	0.080	0.451	1,185	1.00	....
2	..	.....	1,830	99	56	92	128	99	..	...	...	...	...	.....	.....	.....	....	....
3	..	.....	1,730	94	64	98	114	99	..	...	109	566	177	0.078	0.575	2,520	1.30	45.7
4	..	Nausea	1,530	100	62	99	136	99.2	..	...	...	...	...	.....	.....	.....	1.36	....
5	..	.....	1,475	90	59	101	136	99.2	..	...	...	...	...	.....	.....	.....	1.35	....
6	..	.....	1,885	103	59	99	124	99	30	1.4	88	566	223	0.223	0.891	2,020	1.50	....
7	..	.....	1,922	104	59	97	130	99.2	..	...	...	...	...	.....	.....	.....	1.36	....
8	..	.....	.....	103	63	99	126	99.2	..	...	...	...	...	.....	.....	.....	1.30	....
9	..	.....	1,650	104	60	98	133	99.5	..	...	...	...	...	.....	.....	.....	....	44.9
10	..	.....	1,157	101	63	94	114	99	..	...	...	...	...	0.166	0.628	1,380	....	44.8
11	..	.....	1,177	98	65	93	128	99	..	...	...	...	...	0.101	0.626	1,730	1.20	44.7
12	..	.....	1,607	108	60	103	129	99	..	...	...	...	...	0.086	0.569	1,525	....	44.6
13	..	.....	1,630	102	60	97	129	99	24	1.4	92	601	158	0.156	0.728	2,425	1.13	45.0
14	..	.....	1,922	104	60	93	125	99	..	...	...	...	...	0.101	0.597	2,390	....	44.7
15	..	Fatigued	1,965	102	57	96	128	98.8	..	...	...	...	...	0.043	0.691	2,805	1.25	45.2
16	..	.....	1,637	103	60	96	129	98.8	..	...	...	...	...	0.062	0.559	2,340	....	45.4
17	..	.....	1,470	99	61	94	119	99	..	...	...	...	...	0.100	0.518	1,785	....	....
18	..	.....	1,210	100	50	94	120	98.8	..	...	...	...	...	0.077	0.675	2,395	1.05	45.5
19	..	Coryza	1,220	92	50	87	126	98.8	..	...	...	...	...	0.043	0.508	2,540	....	45.7
20	..	Coryza	1,425	95	55	90	112	99	25	1.4	89	604	175	0.040	0.612	2,625	1.10	45.3
21	..	Coryza	1,835	94	62	78	120	99	..	...	...	...	...	0.045	0.590	2,750	....	45.3
22	..	Coryza	1,775	90	58	88	136	98.8	..	...	...	...	...	0.064	0.477	2,005	....	45.5
23	..	Palpitation	1,140	...	...	...	...	98.8	..	...	...	...	...	0.055	0.635	1,840	....	45.3
24	..	Relapse	475	99	58	107	155	98.8	..	...	...	...	...	0.160	0.680	1,560	1.15	45.1
25	..	Relapse	905	104	58	101	132	98.8	28	1.4	68	573	170	0.358	0.762	1,280	....	45.1
26	..	Recovery	....	99	55	97	127	98.8	..	...	...	...	...	0.430	0.697	1,245	1.20	44.3
27	..	Discharged	....	....	..	....	....	.....	..	...	...	...	...	.....	.....	.....	....	44.8
28	..																	

COMMENT

Certain individual points in agreement and certain in disagreement with other writers have appeared from the studies reported. We found the same definite changes in the unmeasurable clinical symptomatology noted in the clinical studies with the Swingle and Pfiffner preparation,[3f] namely, (1) "disappearance of anorexia, nausea, and vomiting, and reappearance of appetite," (2) "relief from fatigue and increase in strength and endurance" and (3) "change in the mental attitude characterized by hope and euphoria." Although the effect of cortin on the appetite was striking, none of our four patients actually gained in weight under treatment.

When one turns to the triad of objective features, asthenia, hypotension, and pigmentation, the findings are less clearcut.

Ergographic Tracings.—Careful tracings were done on the patients while under observation. A priori one would think this might furnish the desired "measuring stick." The results were disappointing. The tracings failed to fluctuate with the patient's condition and were often surprisingly little affected by cortin. Practice and mental attitude are factors that are difficult to control. Thus the patient in case 2 continued to improve as regards the work done, when the evidence as a whole pointed to a general decrease in strength.

Blood Pressure.—When a patient is recovering from a state of shock the blood pressure rises from the extreme low level as a result of the administration of cortin. But the effect of cortin on the low blood pressure in chronic suprarenal insufficiency is less striking. Only in case 2 did the blood pressure seem to respond after many days of treatment. The tendency of the blood pressure in Addison's disease to fall on standing was decreased by cortin.

Pigmentation.—In none of our patients was pigmentation unequivocally decreased. In case 2 it was definitely increased under treatment. A lessening in pigmentation has been reported for the Swingle and Pfiffner preparation [5] and for cortin.[3e] The discrepancy may be due, of course, to difference in extracts, difference in dosage or difference in patients.

Blood Cholesterol.—Influenced by the work of Reiss,[6] we followed the blood cholesterol value carefully. This author suggested that the hormone of the suprarenal cortex in conjunction with the reticuloendothelial system fixes cholesterol from the blood into the tissues, and he reported a lowering of the blood cholesterol as a result of the administration of extract of active suprarenal cortex. Rogoff and

5. Rowntree et al. (footnote 3, *f*). Simpson (footnote 3, *g*).

6. Reiss, M.: Studien über die Funktion der Nebennierenrinde: III. Nebennierenrinde und Cholesterinstoffwechsel, Endokrinologie **7**:1, 1930.

Stewart,[7] on the other hand, found no constant change in the blood cholesterol in adrenalectomized dogs. Our data are interesting but inconsistent. The patient in case 1 had a low blood cholesterol value, which was increased from 44 to 86 mg. per hundred cubic centimeters after a large injection of cortin. The patient in case 2, who had almost daily determinations of blood cholesterol during periods of administration and withdrawal of the hormone, showed an almost constant level. Of ten determinations, the minimum value was 184 mg. per hundred cubic centimeters and the maximum 195 mg. In the patient in case 3 an interesting isolated observation was made. One morning during the third week following the discontinuation of cortin the serum was found to be lipemic, and the blood cholesterol was 367 mg. per hundred cubic centimeters, the previous level having been 120 mg. There was no change in the patient's condition, there had been no change in her diet and the blood cholesterol on the following day was 138 mg. A similar less striking episode occurred in case 4.

Nonprotein Nitrogen.—A lowering of the blood nonprotein nitrogen and creatinine by cortin during acute insufficiency was demonstrated in case 4. This is in agreement with results in animal experimentation. But as measuring sticks these quantities are of value only when the patient is moribund. These values were not affected by cortin in case 2.

Blood Sugar.—In agreement with the results of other investigators, the blood sugar, when low, rose after the injection of cortin (from 35 mg. to 111 mg. per hundred cubic centimeters in case 4), but when normal it was unaffected by cortin (case 3). The average blood sugar during fasting in case 2 (table) rose during the period of withdrawal of cortin from 95 mg. to 126 mg. per hundred cubic centimeters and fell, after treatment was reestablished, to 95 mg. But the significance of the latter change is further complicated by the fact that this patient in the past had suffered from diabetes.

Basal Metabolism.—In no one of our patients was the basal metabolism strikingly low, and cortin was without effect on it.

Electrocardiograms.—Clinical observation and animal experimentation indicate that the hormone of the suprarenal cortex is intimately related to the mechanism of muscular contraction. The low blood pressure and weak pulse of acute suprarenal insufficiency force one to the conclusion that the strength of the ventricular contraction is lessened in this condition. One might suppose that the electrocardiogram would reveal small complexes during states of acute suprarenal

7. Rogoff, J. M., and Stewart, G. N.: Studies on Adrenal Insufficiency. VII. Further Blood Studies (Cholesterol and Calcium) in Control Adrenalectomized Dogs, Am. J. Physiol. **86**:25, 1928.

insufficiency and larger complexes during recovery. In case 4, the electrocardiograms showed no significant variations, as the patient was revived from a state of circulatory collapse and as the pulse and blood pressure rose from almost imperceptible levels to fair strength. The complexes increased in size, but the variations were within the limits of error. In two other cases the electrocardiogram was studied with and without treatment with cortin and no significant variations were found.

Temperature Charts.—Hartman [8] has shown that adrenalectomized rats have less resistance to cold temperatures than do normal rats or adrenalectomized rats treated with cortin. Untreated adrenalectomized rats will show, when placed in a cold environment, a drop in temperature as great as 10 C., and may die following the adventure. Under precisely the same conditions, normal rats or adrenalectomized rats treated with cortin will show a drop of only 2 C. In all probability the suprarenals influence body temperature through the medium of the skeletal muscles. Cold temperatures throw a strain on the heat-regulating mechanism, possibly on the suprarenal cortex. Hartman [9] has demonstrated hypertrophy of the adrenals in normal rats following exposure to such temperatures. In the same manner lowering of the body temperature in cases of Addison's disease might cause additional strain on the residual cortical tissue with resulting relapses. The observations made in cases 3 and 4 seem to bear this out. Both the acute episodes in case 3 and the single acute episode in case 4 were preceded by subnormal temperatures. One cannot say from the data whether the sequence was exposure, subnormal temperature, increased load on the suprarenal cortex and precipitation of acute insufficiency, or whether a subnormal temperature may not be the first indication of insufficiency. The additional observation made in case 3, that the tendency to subnormal temperatures disappeared under treatment with cortin, is likewise in agreement with the results of animal experimentation and is very suggestive. Indeed, a resistance of body temperature to lowering of temperature on exposure may some day be made into that much-to-be-desired clinical measuring stick of suprarenal insufficiency.

The most convincing observations that have resulted from our studies, as regards the benefit of cortin to the patient, were those related to the treatment of the acute collapse of suprarenal insufficiency and the ability of two of our patients so treated to go for long periods without further substitution treatment. One receives the impression

8. Hartman, F. A.: Increased Resistance to Cold Produced by Cortin After Adrenalectomy, Proc. Soc. Exper. Biol. & Med. **28**:702, 1931.

9. Hartman: Personal communication.

that in a patient with perhaps mild chronic suprarenal insufficiency a vicious cycle is set up, for some unknown reason (perhaps exposure to cold), which leads to collapse, and that cortin can break up this cycle. Once the cycle is interrupted the patient may for a considerable period be relatively symptom-free. When the patient with Addison's disease is not having acute symptoms, the efficacy of cortin in the doses employed is less dramatic.

SUMMARY AND CONCLUSIONS

1. Four patients with Addison's disease have been treated with cortin (Hartman's extract). Of these, three were in all likelihood suffering from tuberculosis of the suprarenal glands and one from primary atrophy of the suprarenal cortex. We believe that all the patients received benefit from treatment.

2. A scientific evaluation of the efficacy of treatment is curtailed by the absence of a chemical or physical variable that fluctuates proportionately to the degree of suprarenal insufficiency, and that can be accurately measured.

3. The clinical evaluation of the efficacy of treatment rests chiefly on the following factors: (*a*) disappearance of nausea and vomiting, (*b*) restoration of appetite, (*c*) increase in strength and feeling of well-being and (*d*) prevention of death in acute suprarenal insufficiency (this is the most important).

4. In one patient with acute suprarenal insufficiency in a moribund condition, the administration of cortin alone, without any adjuncts to treatment, produced a dramatic result. The nonprotein nitrogen of the blood was reduced to normal, and the blood sugar was elevated to normal, concomitant with treatment.

5. The effect of cortin on ergographic tracings, blood pressure, pigmentation, blood cholesterol, blood nonprotein nitrogen, blood creatinine, blood sugar, urinary excretion of creatine and creatinine, the basal metabolic rate and electrocardiographic tracings has been studied and discussed. None of these possible variables has been found of value in the following of the fluctuations in the degree of suprarenal insufficiency.

6. The tendency to subnormal temperature was decreased by treatment with cortin. It was further noted that three acute episodes of suprarenal insufficiency were ushered in by subnormal temperatures. The subnormal temperatures may have been the cause or the result of the insufficiency.

7. Cortin has proved of the most value in the treatment of patients who are in a prostrate and moribund condition. Thus in the clinic as in the laboratory the best measuring stick of its efficacy remains the test of life or death.

ADDENDUM

Since this paper was submitted for publication, two more in this group of four patients have died. Only one of the group is still living. A brief summary of the subsequent clinical data and the autopsy observations for these two patients is of importance.

CASE 2 (Mrs. A. D. W.).—After a year of successful treatment with cortin, severe local reactions began to develop in February, 1932, and on February 27 cortin was discontinued. After a brief latent period the patient began to show renewed evidence of suprarenal insufficiency, and in a few days nausea, vomiting and increased pigmentation had developed. A marked stiffness of the hamstring muscles, especially on the left, developed, which suggested localized tetanus. Cortin was given intravenously, and tetanus antitoxin was given intravenously as well as intraspinally. The patient failed to respond to treatment and died on March 9. Her blood pressure was exceedingly well maintained throughout the illness, which at one time made the diagnosis seem questionable. On the day of death the blood pressure was 118 systolic and 80 diastolic. Autopsy revealed tuberculosis of both suprarenals with complete destruction of the glands. Gross and microscopic examination revealed no remaining normal suprarenal tissue.

CASE 4 (Rose M. C.).—The patient was transferred to the Johns Hopkins Hospital on October 28, 1931. Shortly after arriving at Baltimore, she had several successive relapses during which she was treated successfully by extract of the adrenal cortex. Jaundice developed on November 9 and increased steadily. Secondary anemia, bleeding from the gums, edema of the lips and ascites appeared, and the patient died on Dec. 29, 1931. Autopsy revealed Addison's disease of the so-called "cortical atrophy" type, with almost complete destruction of the medulla of both suprarenals.

The trustees of the Massachusetts General Hospital, on behalf of the patients and in the interest of science, put a considerable sum of money at the authors' disposal to help defray the cost of the production of cortin. Dr. Frank A. Hartman, although his limited facilities were taxed to the utmost, met our emergencies as they arose and curtailed his own scientific investigations in order to spare cortin for our patients.

PERICARDITIS

IV. FIBRINOUS PERICARDITIS AND "SOLDIER'S PATCHES"

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Fibrinous pericarditis without effusion is undoubtedly the most common disease of the pericardium. It is the forerunner of many cases of pericarditis with effusion, of purulent pericarditis, and of adherent pericarditis. The uncomplicated form of this disease is probably the most innocuous form of pericarditis. The inflammatory process may involve either the visceral or the parietal layers of the pericardium, or both, and may be localized or widespread in its involvement. A fibrinous exudate occurs, which, when the deposition is marked, results in the "shaggy" or "bread and butter" appearance of the pericardium.

MATERIAL

Fibrinous pericarditis without effusion occurred in sixty-two of 373 cases of pericarditis, an incidence of 16.6 per cent.

These cases occurred in forty-three males (69.4 per cent) and nineteen females (30.6 per cent). It is interesting to observe that the incidence of cases of pericarditis of all groups in males is predominant. The reason for this is not clear.

Virtually all decades of life were represented. There were two patients in the first decade of life, four in the second, five in the third, eight in the fourth, seven in the fifth, sixteen in the sixth, thirteen in the seventh, and seven in the eighth. The youngest patient was only 4 months of age, whereas the oldest was 74 years of age. The average age was 48.2 years. The majority of patients (70.9 per cent) were between the thirtieth and the seventieth year of life.

ETIOLOGY

Intrathoracic infection appeared to be causative of fibrinous pericarditis in thirty-three cases (53.2 per cent). Primary pericarditis of indeterminate bacterial type occurred next in frequency, in twelve cases (19.4 per cent). Rheumatic fever was the apparent cause in nine cases (14.5 per cent), and infection elsewhere in the body in eight cases (12.9

From the Section on Cardiology, the Mayo Clinic.

per cent). Infection, therefore, was the basis of the pericarditis in the majority of instances.

The intrathoracic infections were as follows: pneumonia in fourteen cases (42.4 per cent), empyema in eleven cases (33.3 per cent), pulmonary abscess in four cases (12.1 per cent), pleuritis in two cases (6.1 per cent) and pulmonary tuberculosis in two cases (6.1 per cent).

In all cases in which fibrinous pericarditis was associated with rheumatic heart disease, it seemed justifiable to conclude that rheumatic fever was the etiologic condition.

The cases classed as primary pericarditis occurred in the absence of infection elsewhere in the body and were believed to be examples of direct invasion of the pericardium. Nine cases were associated with recent or healed cardiac infarction.

The cases of fibrinous pericarditis that resulted from infection elsewhere in the body than the thorax comprised four cases of generalized peritonitis, three cases of pyelonephritis, and one case of perforated gastric ulcer.

PATHOLOGY

The weights of the hearts in forty-seven cases (75.8 per cent) were available for study. Two cases were excluded because the patients were children. The average cardiac weight was 409.6 Gm. The smallest heart weighed 200 Gm., whereas the greatest recorded cardiac weight was 793 Gm. The average weight is considerably greater than that of the normal heart, as shown by the studies of Smith;[1] the average normal adult heart of the male weighs 294 Gm., and the average normal heart of the female, 250 Gm. In eleven cases (23.4 per cent) the weight of the heart was between 200 and 299 Gm. Thirty-six patients (76.6 per cent) had cardiac weights in excess of 300 Gm., as follows: fifteen (31.9 per cent), between 300 and 399 Gm.; eight (17.0 per cent), between 400 and 499 Gm.; nine (19.2 per cent), between 500 and 599 Gm.; one (2.1 per cent), between 600 and 699 Gm., and three (6.4 per cent), between 700 and 799 Gm.

The averages are materially influenced by the inclusion of cases with associated cardiac disease, lesions dominant in their influence on cardiac hypertrophy. These cases will be discussed separately in the ensuing text.

Associated Cardiac Disease.—Associated disease of the heart occurred in thirty-one cases (50 per cent). This incidence closely approximates that of associated cardiac disease in cases of adherent pericarditis (53.5 per cent), and greatly exceeds that in cases of pericarditis with effusion (29.2 per cent).

1. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, Am. Heart J. **4**:79 (Oct.) 1928.

Hypertensive cardiac disease occurred with greatest frequency; it was recorded in eleven cases (17.7 per cent). Among these cases, the average cardiac weight was 555.2 Gm.; the smallest, 381 Gm., and the greatest, 793 Gm. The youngest patient was only 18 years of age, the oldest, 72. The average age was 47.9 years.

Coronary disease occurred in ten cases (16.2 per cent) and included nine cases of recent or healed cardiac infarction. The average cardiac weight was 463 Gm. The minimal cardiac weight was 300 Gm., whereas the maximal weight was 709 Gm. Four patients had associated hypertension; with their exclusion, the average weight was 411.6 Gm. The youngest patient was 50 years of age; the oldest, 74. The average age was 64.8 years.

Rheumatic heart disease occurred in eight cases (12.9 per cent). The involvement of valves, with the frequency, was as follows: mitral, three cases; mitral and aortic, three cases; mitral and tricuspid, two cases, and mitral, aortic and tricuspid, one case. The average cardiac weight was 397 Gm.; the smallest was 283 Gm., and the largest, 615 Gm. The age of the youngest patient was 6 years; that of the oldest, 52. The average age was 28.3 years.

Subacute bacterial endocarditis (Streptococcus viridans) occurred in two cases (3.2 per cent), in both instances engrafted on an old mitral lesion. The average cardiac weight was 517.5 Gm., the hearts weighing 505 and 530 Gm., respectively. The patients were 16 and 33 years of age; the average age, then, was 24.5 years.

The average weight of the heart in all cases in which there was associated cardiac disease was 496.3 Gm.

Fibrinous Pericarditis Without Associated Cardiac Disease.—Thirty-one of the cases (50 per cent) were in this subgroup. In these cases, the influence of lesions other than fibrinous pericarditis on cardiac hypertrophy has been eliminated. The average cardiac weight was 251.9 Gm., indicating that the average heart in this group is normal in weight. The smallest heart weighed 200 Gm., whereas the largest weighed 460 Gm. The youngest patient was only 4 months of age, whereas the oldest was 73 years of age. The average age was 49.7 years, almost approximating that of the patients with associated cardiac disease; the latter were an average of 2.9 years younger.

Pleural Fluid.—Fluid appeared in one or both pleural cavities in twenty-two cases (35.4 per cent). The fluid was confined to the right pleural cavity in nine cases and to the left in six cases; it was contained in both in seven cases. It was purulent in eleven cases, exudative in two cases, and transudative in nine cases.

CLINICAL FEATURES

Forty-two patients (67.8 per cent) presented complaints entirely unrelated to the cardiovascular system: carcinoma, six cases; nephritis

and pneumonia, three cases, respectively; cholecystitis, gangrenous appendicitis, hernia, adenomatous goiter, empyema and benign prostatic hypertrophy, each two cases, and vesical calculus, renal calculus, perinephritic abscess, hypernephroma, erythema multiforme, calculus of the common bile duct, miliary tuberculosis, pulmonary tuberculosis, cellulitis of the neck, fracture of the femur, Addison's disease, pulmonary abscess, bronchiectasis, subdiaphragmatic abscess, duodenal ulcer, staphylococcal pyemia, fecal fistula and arsenical poisoning, each one case.

The remaining twenty patients (32.3 per cent) of the sixty-two with fibrinous pericarditis presented complaints directly related to the heart. They all had associated cardiac disease and comprised 64.5 per cent of the group of thirty-one patients who had such associated disease.

The most characteristic physical sign of fibrinous pericarditis is a pericardial friction rub. It may be present but a short time, or its presence may be evanescent. Its recorded incidence in this study was 11.3 per cent.

Electrocardiography.—Electrocardiograms of twelve patients were obtained, all of whom had associated cardiac disease; the resulting abnormalities obviously arose from the primary disease of the heart. In two cases there was incomplete bundle branch block; in five cases, significant T wave negativity; in one case, changes in the R-T segment, and in one case, auricular flutter. In three cases, the electrocardiogram was essentially unaltered.

MODE OF DEATH

Twenty patients (32.2 per cent) died as the result of heart failure; all had associated cardiac disease. Nine patients (14.5 per cent) died of coronary disease; their average heart weight was 326.7 Gm., and their average age was 64.2 years. Hypertensive heart disease was the cause of death in five cases (8.1 per cent); the average weight of the heart was 642 Gm., and the average age of the victims, 49 years. Four patients (6.4 per cent) with rheumatic heart disease died of congestive failure; the average weight of the heart was 428.3 Gm., and the average age, only 25.5 years. The two patients (3.2 per cent) with subacute bacterial endocarditis died of their disease; the average cardiac weight was 517.5 Gm.; the average age was 24.5 years. The average weight of the hearts of the entire group of patients who died of heart disease was 526 Gm., and the average age of the patients, 49.2 years.

The remaining forty-two patients (67.8 per cent) died of causes unrelated to the heart. Sepsis was responsible for the deaths of twenty-two; pneumonia, nine; uremia, five; pulmonary embolism, two; tuberculosis, two; Addison's disease, one, and arsenical poisoning, one. The average cardiac weight in these cases was 354.2 Gm., a value not greatly in excess of normal. The average age of the patients was 49.2 years.

SO-CALLED SOLDIER'S PATCHES

Soldier's patches, or milk spots, are whitish, localized areas found from time to time in the pericardium. They are believed to represent relics of localized, nonobliterating pericarditis. The areas are usually fibrous, but at times hyaline changes are evident. We found records of fifteen cases in which these changes were present. The cases occurred in eleven males (73.3 per cent) and four females (26.7 per cent). The average age of the patients was 47.6 years; the youngest patient was 22 and the oldest 79 years. Only three patients had associated cardiac disease. The average weight of the heart of those without associated cardiac disease was virtually normal, 319.9 Gm. The smallest heart weighed 234 Gm., whereas the largest weighed 427 Gm. The majority of the patients (86.6 per cent) died of causes unrelated to the heart.

It is possible that the so-called soldier's patches, or milk spots, represent the scars of previous, localized, fibrinous pericarditis, but their presence does not seem in any way to interfere with the normal behavior of the heart.

COMMENT AND SUMMARY

Sixty-two cases of fibrinous pericarditis without effusion, in which the patients came to necropsy at the Mayo Clinic, form the basis of this study. There are also comments on fifteen cases in which there were so-called soldier's patches, or milk spots. The incidence in males was greater than that in females.

Associated cardiac disease occurred in thirty-one cases (50 per cent). Although half of the patients had associated cardiac disease, only twenty had complaints fundamentally related to the cardiovascular system. In the majority of cases in which infections occurred either spontaneously or following surgical intervention, disorders unrelated to the heart were present. The predominant clinical features in 32.2 per cent of the cases were referable to the heart. The remaining cases represented a miscellaneous group of diseases. Death from cardiac disease occurred in 32.3 per cent of the cases. In the remaining cases, death was from causes unrelated to the heart.

The weights of the hearts in forty-seven cases were available for study and are discussed.

The major subject of consideration in the etiology of fibrinous pericarditis, as one would anticipate, is an infectious process.

Fibrinous pericarditis appears to be the simplest and most innocuous form of pericarditis. It seems to be prodromal to more serious forms of pericarditis, namely, pericarditis with effusion in some cases, purulent pericarditis in others, and adherent pericarditis in many cases in which the patient survives the etiologic disease.

PERICARDITIS

V. TERMINAL PERICARDITIS

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For many years pathologists have recognized a form of pericarditis which afflicts patients who are dying of debilitating diseases, but which does not appear to be concerned in their deaths. This has been designated "terminal pericarditis."

In considering pericarditis we have attempted to separate our material into groups conforming to pathologic and clinical criteria, so that comparative study would be possible. We appreciate the fact that separation into clearcut types is often difficult, and that some degree of overlapping may occur. We have attempted to show that fibrinous pericarditis without effusion is the simplest form of pericarditis, but have stated that it usually is the forerunner of purulent or of nonpurulent pericarditis with effusion, and of adherent pericarditis.

The accurate segregation of cases of so-called terminal pericarditis is obviously difficult, for it is possible to include cases of fibrinous pericarditis. In order to minimize the possibility of error, we selected, for inclusion in the group of cases of terminal pericarditis, only those in which there was no evidence of healing, in contrast to those placed in the group of fibrinous pericarditis, in which definite attempt at repair was evident. Unfortunately, we cannot report on the bacteriology of these cases at this time, for a separate study by one of our associates [1] has not been concluded. Thus far, it appears that cultures invariably yield negative results.

MATERIAL

In previous studies of this series it has been pointed out that records of 373 cases of pericarditis have been found among records of 8,912 postmortem examinations performed at the Mayo Clinic. Forty cases of terminal pericarditis were found, an incidence of 0.4 per cent in the entire number, and of 10.7 per cent in cases of pericarditis. As with all forms of pericarditis, there were more male than female patients. There were twenty-eight males (70 per cent) and twelve females (30

From the Section on Cardiology, the Mayo Clinic.

1. Work carried on by Dr. H. J. Kullman.

per cent). The youngest patient was 15 years of age; the oldest, 83. The average age was 48.7 years. Only 7.5 per cent of the patients were aged less than 30 years.

PATHOLOGIC DATA

The weights of the hearts in twenty-nine cases (72.5 per cent) were available for study. The average cardiac weight was 377.3 Gm.; the smallest, 250 Gm., and the largest, 650 Gm. In twenty-three cases (57.3 per cent) the weight of the heart exceeded 300 Gm.

Associated Cardiac Disease.—There was a high incidence of associated cardiac disease, twenty-one cases (52.5 per cent), although the heart was predominantly a factor in the clinical syndrome in only four cases.

Hypertensive cardiac disease occurred with greatest frequency, thirteen cases (32.5 per cent). The average weight of the heart was 434.2 Gm. The smallest heart weighed 345 Gm., whereas the largest heart weighed 623 Gm. The average age of these patients was 46.1 years; the youngest patient was 22 years of age, and the oldest, 66.

Coronary disease occurred in three cases (7.5 per cent). The weight of the heart was recorded in only one case, 385 Gm. The average age of these patients was 64.3 years.

Rheumatic heart disease was present in three cases (7.5 per cent); mitral stenosis occurred in two of these cases and marked aortic stenosis in one. The average cardiac weight was 525 Gm., and the average age was 42.3 years.

There was one case (2.5 per cent) of subacute bacterial endocarditis (Streptococcus viridans), the original lesion in which was mitral stenosis. The heart weighed 450 Gm., and the patient was 46 years of age.

One case (2.5 per cent) of hyperthyroid heart disease occurred. The heart weighed 350 Gm., and the patient was only 15 years of age.

The average weight of the heart in all cases in which there was associated cardiac disease was 438.2 Gm.

Terminal Pericarditis Without Associated Cardiac Disease.—There were nineteen cases (47.5 per cent) in which there was no associated cardiac pathologic condition. The average weight of the heart in this group was 302.3 Gm. The smallest heart weighed 250 Gm., and the largest, 400 Gm. Thus, the difference in average cardiac weight between the groups of patients with associated cardiac disease, and those without, was 135.9 Gm.

CLINICAL FEATURES

The major diagnosis in thirteen cases (32.5 per cent) was carcinoma; in the majority of these cases there was metastasis, or extension of the malignant process to contiguous structures. The site of

carcinoma was as follows: stomach, three cases; colon, two cases; bladder, two cases, and esophagus, breast, lung, uterine cervix, larynx and anterior thoracic wall (recurrence), one case each.

Nephritis occurred in ten cases (25 per cent); the majority of the patients died of uremia.

Hyperthyroidism occurred in four cases (10 per cent); these included two cases of exophthalmic goiter and two cases of hyperfunctioning adenomatous goiter. There were two cases with prostatic hypertrophy. The other diagnoses were pneumonia, pulmonary abscess, Addison's disease, subacute bacterial endocarditis (Streptococcus viridans), esophageal diverticulum, gastrocolic fistula, cellulitis of the leg, pernicious anemia, septicemia, uterine fibromyoma and rheumatic heart disease with aortic stenosis, each in one case.

Although the primary diseases in cases in which terminal pericarditis occurred cover a wide range, carcinoma and nephritis together comprised 57.5 per cent.

Infections occurred in twenty cases (50 per cent), an incidence distinctly less than that in the other forms of pericarditis. Associated intrathoracic infection occurred in twelve cases (30 per cent) and comprised pneumonia alone, seven cases; pneumonia and empyema together, two cases, and empyema alone, suppurative mediastinitis and purulent bronchitis, each one case. Infections elsewhere in the body occurred in eight cases (20 per cent) and included such diseases as peritonitis, pyelonephritis, cellulitis and ulcerative colitis.

CAUSE OF DEATH

Only four patients (10 per cent) died as the result of cardiac disease. Three of these died of congestive heart failure and one of subacute bacterial endocarditis. The remaining patients died of the following causes: nephritis, eleven cases; pneumonia, seven cases; peritonitis, five cases; hyperthyroidism, two cases; Addison's disease, one case; pulmonary embolism, one case; ulcerative colitis, one case, and sepsis elsewhere in the body, eight cases.

COMMENT

From this study it appears that the condition designated as terminal pericarditis in some respects does not differ materially from that seen in certain cases of acute fibrinous pericarditis. Our ground for distinguishing between the two conditions has been explained. Terminal pericarditis occurs with greatest frequency in cases in which the primary disease is of long standing and results in progressive debility. This is particularly exemplified by the high incidence of carcinoma and nephritis. That the pericarditis is noninfectious in the majority of

cases is possible, but definite proof of this is still lacking. Identification of terminal pericarditis rests almost wholly on postmortem examination.

SUMMARY

A condition classified as terminal pericarditis occurred in forty of 373 cases of pericarditis, an incidence of 10.7 per cent. A marked predominance of the incidence in males occurred.

Among the major clinical diagnoses in the cases comprising this group, those of carcinoma and nephritis predominated.

Associated cardiac disease occurred in twenty-one cases (52.5 per cent).

Death from heart disease occurred in only 10 per cent of the cases. In the remaining cases, 90 per cent of the patients died of causes unrelated to the heart.

Pleural fluid was present in 35.4 per cent of the cases, an accessory diagnostic sign suggesting the possibility of pericardial involvement.

SEDIMENTATION RATE OF BLOOD CORPUSCLES IN SYNOVIAL FLUID AND IN PLASMA

METHOD OF ESTIMATION AND SIGNIFICANCE IN ARTHRITIS

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Synovial fluids show marked differences of suspension stability. Some are rendered clear by short centrifugation, while others still contain corpuscles after prolonged action of the centrifuge. This is suggestive of differences in composition, and an investigation appeared to be pertinent from a theoretical and a clinical point of view. The value of the sedimentation rate of blood corpuscles in plasma for the differential diagnosis of arthritis is limited by the interference of various factors. By simultaneous estimation in the synovial fluid, it was hoped to eliminate some nonspecific elements and to increase the diagnostic value of the sedimentation speed in arthritis. This program required a method of suspending an amount of corpuscles in synovial fluid equal to that in blood and a suitable technic for the comparative sedimentation test.

TECHNIC

Preparation of the Suspension of Blood Corpuscles in Synovial Fluid.—Into a graduated centrifuge tube is put 2 cc. of 3.8 per cent sodium citrate solution, and then the amount is increased to 10 cc. with synovial fluid. Into a second graduated centrifuge tube 3 cc. of the sodium citrate solution is put, and venous blood is added to 15 cc. The amount can be reduced in the ratio of 1 part of citrate to 4 parts of synovial fluid or blood; the minimum required is 5 cc. of citrated synovial fluid and 10 cc. of blood, however. Six cubic centimeters of the citrated blood is then transferred to a separate test tube and centrifugated at a high speed, simultaneously with the citrated synovial fluid. After ten minutes of centrifugation, the tube containing blood is marked at the level of separation of the corpuscles from the serum. A second mark identifies the upper level of the plasma. In order to be assured that the separation of the cells and plasma is complete, I recentrifugate until there is no change in the level of the cells. The synovial fluid is centrifugated till the supernatant layer is clear. The plasma is then separated carefully from the corpuscles with a pipet, and an equal amount of centrifugated synovial fluid is substituted, to the upper mark. This procedure secures a suspension of corpuscles in synovial fluid equal to that in the citrated blood (fig. 1).

The Set-Up of the Sedimentation Test.—Two 5 cc. pipets are marked at a height of 20 cm. from the tip. Holes to a depth of about 5 mm. are bored in large rubber stoppers (no. 10).

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* Frederick Brown Research Fellowship, Hospital for Joint Diseases.

The suspension of corpuscles in the synovial fluid and the remainder of the original citrated blood are now shaken until thoroughly mixed. Each is then drawn into a pipet to the mark and set up vertically in a rubber stopper; plasticine can be used for this purpose, if desired. At intervals of one hour, marks are made at the level of separation of the corpuscles from the clear fluid. Final readings are made in twenty-four hours (fig. 2).

This method follows the Westergreen technic except for two modifications: (1) citrate is accurately measured into tubes instead of being drawn into syringes; (2) the pipets are of larger caliber because of the higher viscosity of the synovial fluids. Finally, more readings were made than in the routine tests, in order to secure more data.

CONTROLS

In order to establish the adequacy of the technic, the following experiments were carried out:

1. In a number of cases, the sedimentation was interrupted after several hours, the corpuscles were resuspended, and the sedimentation was carried out a second time. The readings were found to be practically identical.

2. Tests were carried out with both unwashed corpuscles and corpuscles washed in saline. It was found that the sedimentation rates did not deviate; washing of the corpuscles was therefore abandoned.

3. Corpuscles from the blood of three different patients were suspended in three portions of the same synovial fluid in the ratio of 30 per cent of corpuscles to 70 per cent of fluid. The sedimentation curve showed an identical character in the different suspensions, although the single values varied. This proves that synovial fluid itself is largely responsible for the character of the sedimentation.

4. It was proved that neither centrifugation nor shaking has any marked influence on the sedimentation rate.

SUPPLEMENTARY TESTS

The viscosities of the citrated synovial fluid and plasma were determined in nearly all cases. A cell count, a differential count, Wassermann and gonococcus complement fixation, cultures and an estimation of the icterus index were made on each synovial fluid. A sedimentation by the standard Westergreen method was carried out on the remaining blood, and although somewhat higher values were found in the first hour in a great number of cases, the general character of the curve remained unchanged.

COMPARISON OF SEDIMENTATION CURVES

The determination of the normal sedimentation curve is necessary before pathologic changes are considered. It is simple to establish the sedimentation of normal blood; the amount of synovial fluid, however,

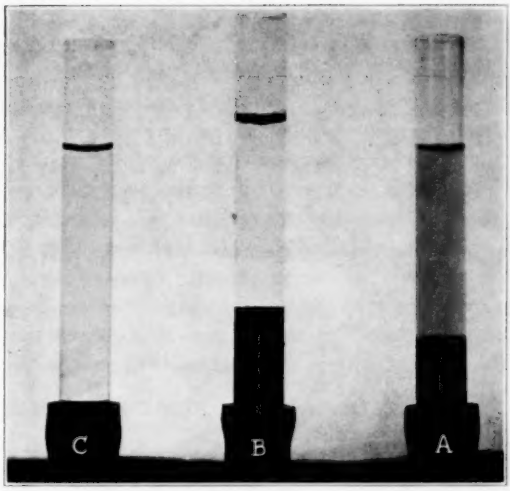

Fig. 1.—Preparation of blood and synovial fluid for the comparative sedimentation test. *A*, centrifugated citrated blood; *B*, plasma pipetted off, with the upper and lower level marked for substitution by synovial fluid; *C*, centrifugated citrated synovial fluid.

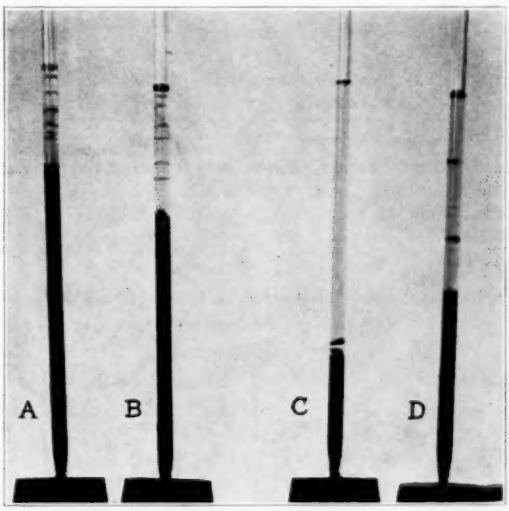

Fig. 2.—Comparative sedimentation of blood and synovial fluid. *A* and *B*, normal sedimentation of blood (*A*) and synovial fluid (*B*) from a case of osteoarthritis. *C* and *D*, highly increased sedimentation in blood (*C*) and synovial fluid (*D*) in a case of gonorrheal arthritis. Each mark indicates an interval of one hour. The sedimentation in twenty-four hours is shown by the column of clear fluid.

in normal joints is not sufficient for the test. I have therefore substituted noninflammatory synovial effusions that showed a composition approaching the normal fluid. Figure 3 represents the average sedimentation curve in eight cases of chronic arthritis due to irritation by preceding trauma or degenerative changes of the articular surfaces (ostearthritis). The history, appearance and bacteriologic examination did not reveal an inflammatory factor, and the sedimentation of blood was normal. The synovial fluid showed a high viscosity and high mucin content, a low cell count and a prevalence of synovial lining cells, properties that preceding studies [1] have shown to be characteristic for normal synovial fluids. The curve of the synovial fluids shows, in comparison to that of the blood, the very slow start of the sedimentation and the

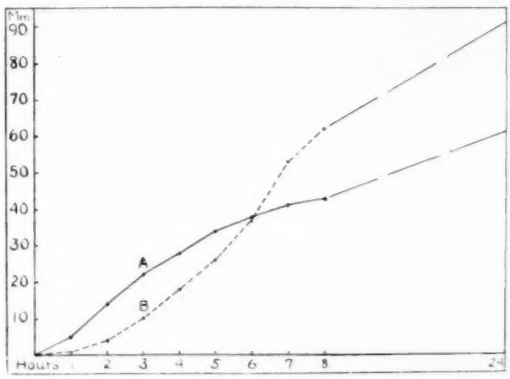

Fig. 3.—Standard comparative sedimentation curve, on the basis of eight cases of chronic noninflammatory (oste) arthritis. Normal blood sedimentation (*A*) and slow sedimentation of synovial fluid (*B*). The comparative sedimentation index was 5.26 per cent.

gradual increase after the first hour; the curve for blood is crossed after six hours. This initial delay and subsequent increase of sedimentation were observed in fifteen other noninflammatory effusions (fig. 3).

The composition of normal synovial fluid explains the remarkable course of sedimentation. Synovial fluid contains a low percentage of protein, especially globulins and fibrinogen, which initiate and increase sedimentation; the start of the sedimentation is therefore slower than that in the blood. On the other hand, the mucinous substance in synovial fluid raises its viscosity far above blood plasma and probably brings about the subsequent increase of the sedimentation above that of normal blood.

1. Kling, D. H.: The Nature and Origin of Synovial Fluid, Arch. Surg. **23**:543 (Oct.) 1931.

COMPARATIVE SEDIMENTATION INDEX

Westergreen and his followers consider the reading after the first hour to be the most important. By the modification outlined, the average sedimentation of normal blood in the first hour amounts to 4.75 mm., with a high normal of about 10 mm. The study of an average sedimentation curve of noninflammatory synovial fluid demonstrates that an initial delay, with an average value of 0.25 mm. and a maximum of 2 mm., after the first hour, is characteristic and is produced by the composition of normal synovial fluids. The ratio of the readings after one hour for synovial fluid and plasma represents, therefore, a comparative index of the sedimentation in both fluids. This is expressed in percentage in the following formula:

$$\text{Comparative sedimentation index (after one hour)} : \frac{\text{Reading of synovial fluid}}{\text{Reading of blood}}$$

$$\text{For standard curves, C.S.I.} = \frac{0.25}{4.75} \text{ or } 5.26 \text{ per cent.}$$

Any change that influences the sedimentation in plasma or synovial fluid must alter this equation.

ANALYSIS OF MATERIAL

The comparative sedimentation was carried out in sixty-one cases of arthritis; the distribution of the various types is given in table 1.

TABLE 1.—*Summary of Material*

Types	Number of Cases
Acute nonspecific and gonorrheal arthritis	10
Tuberculous arthritis	2
Syphilitic arthritis	3
Chronic infectious arthritis	5
Chronic rheumatoid (atrophic) arthritis	8
Traumatic arthritis	6
Posttraumatic arthritis	13
Osteoarthritis (hypertrophic)	14
Total	61

Acute Infectious Arthritis (*Table 2*).—This group contains ten cases. The sedimentation was carried out from five days to four weeks after the onset of the condition. Eight patients had arthritis for the first time; in six cases one knee joint was involved, and in four cases, several joints. In three cases the gonorrheal etiology was established by culture, smear or gonococcus complement fixation in the synovial fluid; in two others, gonococci were found in the prostate and uterine cervix, respectively. The etiology in five cases was regarded as nonspecific; cultures and serologic tests of the joint fluids gave negative results. In these cases, the tonsils, teeth or uterus was infected, and the condition of the joints followed influenza or tonsillitis. Puerperal sepsis was responsible in one case.

The number of cells in the fluid varied from 4,880 to 120,000 per cubic centimeter; the percentage of polymorphonuclear leukocytes was from 59 to 95.

The viscosity of the citrated fluid ranged from 3 to 13, and the viscosity of the citrated plasma, from 1.4 to 2.4.

The average sedimentation curve for this group (fig. 4) is characterized by the high values after the first hour and by the rapid course of the sedimentation, which was almost complete after three hours in the blood and after four hours in the synovial fluid. On account of its initial high sedimentation, the curve for the blood is not crossed by that

TABLE 2.—*Acute Infectious Arthritis (Nonsyphilitic and Gonorrheal)*

Case	Name	Diagnosis	Duration, Days	Sedimentation After 1 Hour		C.S.I.,* per Cent	Viscosity of Fluid	Comment
				Blood	Fluid			
1	A. S.	Polyarthritis (?)	28	116	79	68.1	4.2	Gonococci in cervix
2	J. L.	Gonorrheal of right knee	5	69	45	65.2	5.4	Wassermann gonococcus complement fixation 4+; culture positive for gonococci
3	S. L.	Gonorrheal of right knee	14	44	19	43.2	4.1	Smear positive for gonococci
4	S. G.	Septic polyarthritis	14	32	9	28.1	...	After puerperal fever
5	L. A.	Nonspecific of left knee	14	78	22	28.2	...	Teeth infected
6	W. B.	Nonspecific of right knee	7	100	25	25.0	3.0	Cervical adenitis (streptococcic) 3 years before
7	T. S.	Gonorrheal of left knee	3	107	25	23.4	5.8	Gonococcus complement fixation 2+; smear positive for gonococci
8	J. K.	Nonspecific polyarthritis	14	108	23	21.3	4.8	Influenza
9	A. W.	Nonspecific of right knee	4	117	10	8.5	13.0	
10	S. G.	Polyarthritis (?)	7	103	7	6.8	12.8	Gonorrheal arthritis 20 years ago; gonococci in prostatic smear

* In this and the succeeding tables, C.S.I. indicates the comparative sedimentation index.

for the synovial fluid. One exception occurred in a case of gonorrheal arthritis, in which, after two hours, the fluid registered 102 mm. and the blood only 85 mm.

Comment: The rapid sedimentation in both blood and synovial fluid is produced by the increase of the proteins, especially fibrinogen, which in turn is caused by the inflammatory process.

Bauer and his associates [2] calculated the total protein content of normal synovial fluid in cattle to be 0.68 per cent; I have found, in an acute case of gonorrheal arthritis, a total protein content of 6.43 per cent, of which the globulins amounted to 4.13 per cent.

2. Bauer, Walter; Bennett, G. A.; Marble, Alexander, and Chaflin, Dorothy: Observations on Normal Synovial Fluid of Cattle: I. The Cellular Constituents and Nitrogen Content, J. Exper. Med. **52**:835, 1930.

The sedimentation rate in the synovial fluid reflects, therefore, the degree of inflammation of the aspirated joint, while the systemic reaction determines the sedimentation speed of the blood.

The comparative sedimentation index reveals the share that the local process contributes to the general reaction.

In this group, the average sedimentation index is 30.3 per cent, the minimum being 6.8 per cent and the maximum 68 per cent. However, only two cases (cases 9 and 10) had a comparative sedimentation index lower than 21 per cent. The variations in the index are due to the opposite effects of the fibrinogen and mucin on the initial sedimentation; the first increases and the second decreases the initial sedimentation

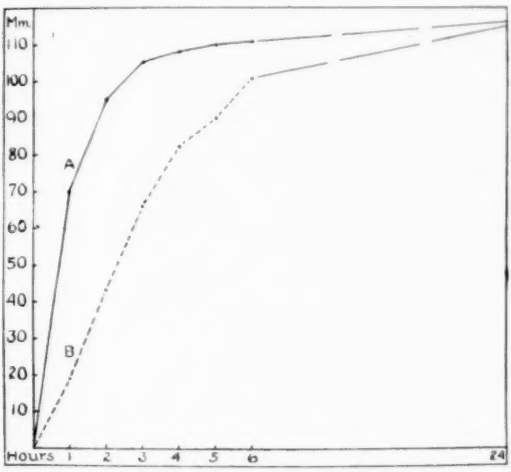

Fig. 4.—Average comparative sedimentation curves in ten cases of acute nonspecific and gonorrheal arthritis. *A* is the curve for blood, and *B*, for synovial fluid. The comparative sedimentation index was 30.3 per cent.

speed. A low sedimentation index can therefore be produced either by a small content of protein or by a high content of mucin. The first occurs when the joint is only slightly inflamed; the second when the inflammation of the synovial membrane leads to a hypersecretion of mucinous substance.

Determination of the viscosity of the synovial fluid permits a differentiation of the causative factor of the low sedimentation index. Effusions of low protein and mucin content have also a low viscosity. Fluids with a high mucin content have a high viscosity. Cases 9 and 10 show the highest viscosity in this group. Their low sedimentation index is therefore caused by a higher content of mucin.

Chronic Infectious Arthritis (Table 3 and Fig. 5).—This group contains five cases of monarticular arthritis. The condition of the joints followed a rectal abscess in one case and osteomyelitis in another case; in three cases no etiology other than exposure to cold was discovered. The duration of the symptoms varied from one to five years. The number of cells in the effusion varied from 4,400 to 43,000, and the percentage of polymorphonuclear leukocytes, from 18 to 88. The viscosity of the citrated fluid ranged from 5.4 to 8; the viscosity of the citrated plasma, from 1.4 to 2.1. In case 1, of five years' duration, an inert streptococcus was cultured from the synovial fluid; in the others the

TABLE 3.—*Chronic Infectious Arthritis (Nonspecific, Cases 1 to 5; Tuberculous, Cases 6 and 7; Syphilitic, Cases 8, 9 and 10).*

Case	Name	Effusions	Duration	Sedimentation After 1 Hour		C.S.I. per Cent	Viscosity of Fluid	Comment
				Blood	Fluid			
1	E. M.	Right knee	5 years	22	12	54.5	5.4	Old osteomyelitis; septicemia*
2	E. P.	Left knee	2 years	21	10	47.6	8.0	Syphilis latens
3	H. M.	Left knee	1 year	50	11	22.0	...	Cold after bathing
4	J. R.	Left knee	Indefinite	37	6	16.2	5.6	Rectal abscess 3 years ago
5	B. K.	Left knee	2 years	50	6	12.0	6.4	Colds
6	R. G.	Left knee	1½ years	30	18	30.5	5.6	Inoculation into guinea-pig positive for tuberculosis
7	M. G.	Left knee	5 days	43	3	6.9	...	Inoculation into guinea-pig positive for tuberculosis
8	A. W.	Right knee	2 years	35	19	54.3	3.2	Wassermann reaction of blood 4+; fluid 3+
9	W. S.	Right knee	3 weeks	13	6	46.2	16.4	Wassermann reaction of blood and fluid 3+
10	E. B.	Both knees	13 years	20	3	15.0	7.0	Wassermann reaction of blood and fluid 4+

* Inert streptococci in synovial fluid.

cultures were negative. All cases still showed signs of activity. The sedimentation curves show a moderate increase in the sedimentation in plasma and synovial fluid. The course of the sedimentation is gradual. In the first two cases the curve for the blood was crossed by that for the synovial fluid after three and four hours, respectively. The average comparative sedimentation index is 25 per cent, the minimum 12 per cent and the maximum 54.7 per cent. The significance of the variations of the index was fully discussed previously.

A high comparative sedimentation index in this group of monarticular arthritis indicates that the involvement of the joints is responsible for the elevation of the sedimentation of blood; a low index points to the presence of other foci. The group as a whole shows a decline of the systemic and a prevalence of the local reaction.

Tuberculous Arthritis.—The comparative sedimentation was carried out in two cases of monarticular tuberculosis of the knee joint (table 3, cases 6 and 7). The sedimentation rates, although somewhat higher, are of the general character of those in the group of chronic infectious arthritis. The comparative sedimentation index is 7 and 30 per cent. respectively.

Syphilitic Arthritis.—Three cases of monolateral and bilateral arthritis of the knee joints were diagnosed as syphilitic on the basis of positive Wassermann reactions and the roentgen and clinical findings (for data, see table 3, cases 8, 9 and 10). The sedimentation curves are somewhat lower than those in the group of chronic infectious

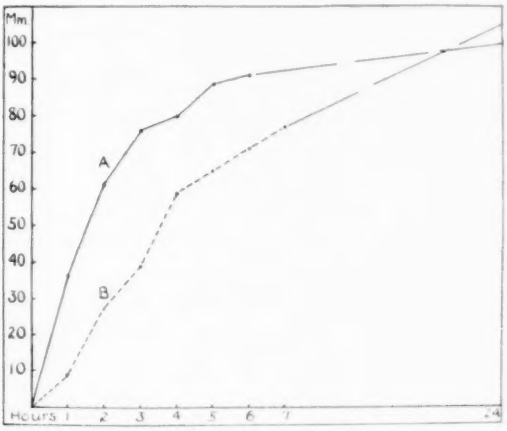

Fig. 5.—Average comparative sedimentation curves of the blood (*A*) and synovial fluid (*B*) in five cases of chronic infectious arthritis. The comparative sedimentation index was 25 per cent.

arthritis. The comparative sedimentation index varies from 15 to 54 per cent. Numerous investigators have found that the sedimentation rate of the blood is increased in secondary and tertiary syphilis. My method demonstrated that in syphilitic arthritis the local process in the joint is probably to a large degree responsible for the increase in sedimentation.

Chronic Rheumatoid (Atrophic) Arthritis (Table 4).—This group is represented by eight cases of polyarthritis. Besides large joints, the small joints of the hands and feet were involved at an early stage, and the condition was frequently bilateral. The onset was insidious and mostly before middle age. The duration varied from one to twenty years. No history of preceding infection was given. Tonsillectomy and extraction of teeth in several cases and mastoidectomy in one case

did not check the progress. In each instance, one or more joints showed signs of active involvement. In each case, one knee joint was aspirated.

The effusions were turbid, with a cell count of from 13,200 to 34,400, and a range of polymorphonuclears from 10 to 86 per cent. Cultures, inoculations into guinea-pigs and Wassermann and gonococcus complement fixations gave negative results. The viscosity of the synovial fluids varied from 3 to 16.8, and that of the plasma from 1.3 to 2.4. The sedimentation curves are high and rank next to those in the acute cases. The comparative sedimentation index is 27.6 per cent, with a minimum of 5 per cent and a maximum of 59 per cent (fig. 6).

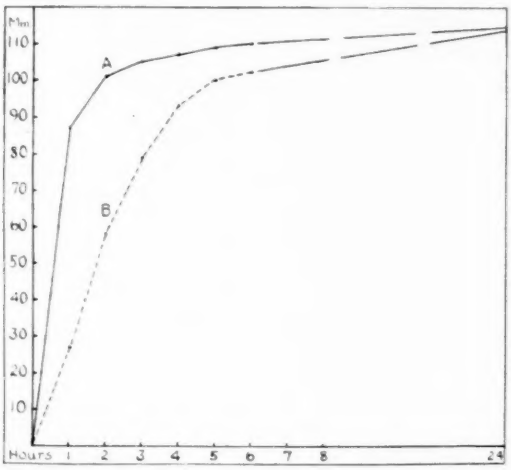

Fig. 6.—Average comparative sedimentation curves of the blood (*A*) and synovial fluid (*B*) in eight cases of chronic atrophic (rheumatoid) arthritis. The comparative sedimentation rate was 27.6 per cent.

In this group of chronic, progressive polyarthrtis, the sedimentation speed of the blood illustrates the general reaction and the comparative sedimentation index reflects the severity of the involvement of the aspirated joint. Case 1 showed a relatively slight increase in the sedimentation of blood; clinically, only the aspirated joint showed activity. The high comparative sedimentation index and viscosity (8.6) indicate that a combination of exudative and hypersecretory reactions is present.

The other seven cases showed a high sedimentation of blood and active involvement of several joints at the time of aspiration. In five cases, the high comparative sedimentation index indicates a severe exudative, inflammatory reaction in the aspirated joint. In two cases, a low index shows that a hypersecretory process prevails. Accordingly,

these cases (table 4, cases 7 and 8) show high viscosity due to an increase of mucin.

Traumatic Arthritis.—This group includes six cases of recent hemorrhagic effusions (table 5 and fig. 7). The sedimentation rates show some increase in three cases (cases 2, 5 and 6). The average sedimentation index is 64.7 per cent, with a maximum of 183 per cent and a minimum of 34.6 per cent. In none of the cases was there perfect agreement between the sedimentations in blood and fluid or in the viscosities.

TABLE 4.—*Chronic Rheumatoid Arthritis*

Case	Name	Diagnosis	Duration, Years	Sedimentation After 1 Hour		C.S.I., per Cent	Viscosity of Fluid	Age, Years
				Blood	Fluid			
1	M. H.	Polyarthritis	2	27	16	59.2	8.6	26
2	M. B.	Polyarthritis	19	67	38	56.7	7.0	29
3	H. A.	Polyarthritis	1	93	39	41.9	3.0	37
4	F. N.	Polyarthritis	20	56	15	26.8	4.4	61
5	C. V.	Polyarthritis	10	100	25	25.0	4.6	44
6	M. B.	Polyarthritis	1½	45	7	15.5	8.8	50
7	J. L.	Polyarthritis	8	69	9	13.0	16.0	33
8	A. D.	Polyarthritis	15	100	5	5.0	16.8	63

TABLE 5.—*Traumatic Arthritis*

Case	Name	Diagnosis	Duration	Sedimentation After 1 Hour		C.S.I., per Cent	Viscosity of Fluid	Comment
				Blood	Fluid			
1	C. D.	Effusion of right knee	1 day	6	11	183.3	6.4	
2	M. B.	Effusion of left knee	2 weeks	13	14	108.0	2.2	
3	S. M.	Effusion of right knee	4 days	9	7	78.0	8.0	
4	H. S.	Avulsed fracture of right knee	2 days	6	4	66.6	6.0	
5	H. T.	Avulsed fracture of left knee	10 days	25	10	40.0		
6	M. C.	Avulsed fracture (?) of left knee	1 day	26	9	34.6	2.6	Roentgenogram negative; fat positive in synovial fluid

This indicates that even recent hemorrhagic effusions contain some component besides blood. Preceding studies on precipitation phenomena in synovial fluids [1] have demonstrated that almost immediately after injury irritation of the synovial membrane leads to hypersecretion and admixture of mucin to the blood.

The increase of the sedimentation of the blood in cases 5 and 6 (table 5) may be due either to some focus of infection unrelated to the injury or to an irritation due to the absorption of broken down blood. The increase in the sedimentation of the fluid, on the other hand, with the rise of the comparative sedimentation index to over 100 per cent in

cases 1 and 2 (table 5) indicates a local reaction on the basis of an increased metabolism, owing to disintegration of the blood or irritation.

Posttraumatic Arthritis (Table 6, Fig. 8).—Thirteen cases of unilateral arthritis of the knee joint were included in this group on the basis of the following criteria: slight or old trauma, occupational or static strain and absence of specific or nonspecific infectious etiology. Osteochondritis dissecans was found in one case; all other roentgen examinations gave negative results.

The duration of the process ranged from one week to three years. In five cases, the effusion showed a slight admixture of blood; in three cases, the icterus index was higher than 6. The number of white cells varied from 500 to 17,600; the percentage of polymorphonuclear leuko-

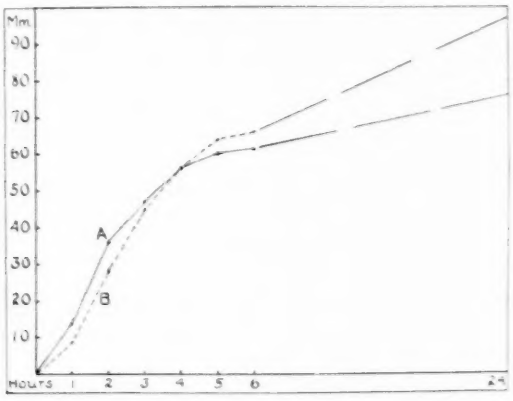

Fig. 7.—Average comparative sedimentation curves of the blood (*A*) and synovial fluid (*B*) in six cases of traumatic arthritis. The comparative sedimentation index was 64.7 per cent.

cytes, from 0 to 60 per cent; the viscosity of the fluid, from 3.7 to 23.6, and that of the blood, from 1.3 to 2. The whole group shows little systemic reaction as the sedimentation rate of the blood was normal in ten cases and only moderately increased (from 19 to 26 mm. in the first hour) in three cases. The sedimentation curve of the synovial fluid, on the other hand, shows the greatest variation with a comparative sedimentation index from 0 to 330 per cent.

In the first three cases (table 5) the sedimentation of the fluid is higher than in the blood. As in the traumatic effusions, this behavior is probably due to increased local metabolism.

In five cases, the sedimentation in the blood and that in the synovial fluid almost correspond, and in two cases, the sedimentation of the synovial fluid is slow, while the viscosities are high. This variation in

the sedimentation of synovial fluid in ten cases with normal sedimentation in blood is presented in figure 8.

Ostearthritis (Hypertrophic—Table 7 and Fig. 9).—This group of fourteen patients suffered chiefly from bilateral arthritis of the knees, with deformities and pain and grating on motion. The duration ranged from several months to eight months. Roentgenograms showed osteoarthritic changes with lipping and spur formation of the articular surfaces. In one case, loose osteochondritic bodies were found in the knee joints. However, pain, swelling and effusion were more conspicuous in one joint. In seven cases, the onset of disability was recent and rather sudden; three of these patients gave a history of strain. In two cases, the effusion developed during physical therapy. The cell count varied from 200 to 32,000 per cubic millimeter, but only two cases

TABLE 6.—*Posttraumatic Arthritis*

Case	Name	Effusion	Duration	Sedimentation After 1 Hour		C.S.I., per Cent	Viscosity of Fluid	Comment
				Blood	Fluid			
1	H. M.	Left knee	1 mo.	3	10	333.3		
2	R. K.	Right knee	6 weeks	4	6	150.0	3.7	
3	C. D.	Left knee	2 mos.	9	10	111.0	6.6	Occupational strain
4	S. H.	Right knee	1 mo.	4	4	100.0	23.6	
5	I. M.	Left knee	1 week	6	6	100.0	5.8	Hematin particles in fluid; occupational strain
6	F. M.	Left knee	6 mos.	6	6	100.0	9.7	
7	S. S.	Right knee	3 years	12	11	92.6	3.9	
8	C. N.	Left knee	1 year	3	2	66.6	10.0	Occupational strain
9	S. R.	Left knee	6 weeks	4	0	0	12.0	
10	E. B.	Left knee	11 days	9	0	0	15.0	Repeated falls, last 11 days previously
11	C. W.	Left knee	7 years	26	8	30.8	14.4	Occupational strain
12	F. B.	Left knee	3 years	25	6	24.0	8.0	Kicked 2 days before
13	A. P.	Left knee	1 week	19	3	15.8	6.0	Osteochondritis dissecans; syphilis latens

showed a count higher than 2,000. The number of polymorphonuclear leukocytes ranged from 5 to 35 per cent. In one case the fluid was slightly hemorrhagic, with an icterus index of 13, although the history did not reveal preceding trauma; in five cases, brown hematin particles were found in the fluid, which were remnants of an old hemorrhage. The viscosity of the fluid varied from 6 to 56, and that of the blood, from 1.3 to 2.2. Wassermann and gonococcus complement fixation tests gave negative results. Only one case gave a positive culture of streptococcus (table 7, case 7).

The sedimentation rate of the blood was normal in only three cases (table 7, cases 1, 2 and 3). In five cases the sedimentation in the blood was increased from 12 to 25 mm.; and in seven cases, from 35 to 58 mm., after the first hour. I have found this increase in sedimentation in the blood in a large percentage of ostearthritic cases, contrary to a number of authors who regard a normal sedimentation rate to be the rule in this condition. The value of sedimentation of the blood for differentiation of hypertrophic from infectious types is therefore

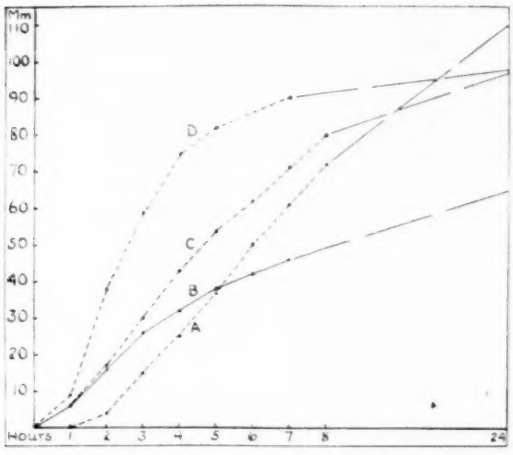

Fig. 8.—Variations in the sedimentation of fluid in ten cases of posttraumatic arthritis with normal sedimentation of blood. *A* shows the low sedimentation of fluid in cases 9 and 10. *B* is the curve for the sedimentation of blood. *C* shows the average sedimentation of fluid in cases 4, 5, 6, 7 and 8. *D* shows the high sedimentation of fluid in cases 1, 2 and 3.

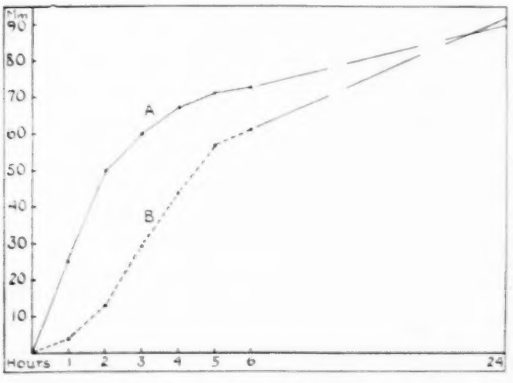

Fig. 9.—Average comparative sedimentation curves of the blood (*A*) and synovial fluid (*B*) in fourteen cases of osteoarthritis (hypertrophic). The comparative sedimentation index was 14.4 per cent.

limited. The sedimentation rate in seven effusions ranged from 0 to 3 mm., and in the other half from 5 to 10 mm. after one hour.

The average comparative sedimentation index was 14.4, with a minimum of 0 and a maximum of 72.7 per cent. A low comparative sedimentation index was found in this group, both with normal and with increased sedimentation in the blood. In the latter case, this indicates that the general reaction is independent of the involvement of the joints. A high sedimentation index, on the other hand, with moderate increase in sedimentation in the blood, points to the arthritic process as the main source of the reaction, due either to secondary infection (case 7, streptococcus) or to the breaking down of hematoma. Further support of this conception is the relatively low viscosity of the fluid in the cases with a high comparative sedimentation index (table 7, cases 7 and 8).

TABLE 7.—*Osteoarthritis*

Case	Name	Effusion	Duration	Sedimentation After 1 Hour		C.S.I., per Cent	Viscosity of Fluid	Age, Years	Comment
				Blood	Fluid				
1	J. B.	Right knee	7 mos.	4	0	0	40.0	44	Old psoriasis
2	L. H.	Right knee	?	11	0	0	48.0	45	Slipped; effusion 4 days later
3	S. N.	Left knee	7 yrs.	12	0	0	44.0	48	
4	H. H.	Left knee	Uncertain	17	5	29.4	18.0	53	Effusion 2 weeks
5	R. W.	Right knee	2 yrs.	14	5	35.7	10.8	42	Depressed arches
6	B. E.	Left knee	5 mos.	16	6	37.5	8.6	48	Knock knees
7	R. C.*	Right knee	7 yrs.	14	10	71.4	8.6	66	Free joint bodies; effusion 2 weeks
8	N. M.	Right knee	2 yrs.	11	8	72.7	8.0	50	Effusion 4 months
9	R. A.	Left knee	3 mos.	25	0	0	56.0	43	
10	C. P.	Right knee	3 mos.	35	0	0	18.0	57	Effusion after diathesis
11	S. A.	Right knee	5 yrs.	45	2	4.4	12.4	55	
12	S. S.	Left knee	7 yrs.	45	3	6.6	15.6	45	Effusion 1 month
13	S. B.	Right knee	?	47	6	10.6	13.6	50	Effusion after baking 1 month
14	I. H.	Left knee	8 yrs.	58	7	13.7	6.0	50	Injury 8 years previously; frequent falls

* Streptococcus found in both smear and culture.

SUMMARY

In a previous study, I have demonstrated that over 90 per cent of synovial effusions have a dual composition. The systemic reaction produces extravasation of proteins and crystalloids from the circulation; the local irritation of the synovial membrane, on the other hand, leads to the secretion of a mucinous substance, which determines the physiochemical properties of the joint fluid. It produces precipitation phenomena with acids in the form of sacs and tubes; it is responsible for the high viscosity and p_H values of the synovial fluid.

The present study has revealed the antagonistic influence of the two different fractions on the suspension stability of the joint fluids. The blood proteins, especially the fibrinogen, increase; the mucin delays the initial sedimentation speed of the corpuscles in the fluid. The observation of differences in suspension stability, which prompted this investi-

gation, is therefore explained by the differences in distribution between the two components of the synovial fluid. An attempt was made to utilize this reaction for the recognition of the type and degree of involvement of the joints in different forms of arthritis.

CONCLUSIONS

A method for the comparative estimation of the sedimentation rate of blood corpuscles in synovial fluid and plasma was developed by replacing the plasma by equal volumes of fluid.

The ratio of sedimentation of blood corpuscles in synovial fluid and plasma after one hour was found to be significant and can be expressed by the comparative sedimentation index.

On the basis of a study of sixty-one cases of arthritis by this method, the following conclusions were drawn:

The severity of an infection of the joint is indicated by the sedimentation curve in the synovial fluid; the general reaction is reflected in the blood curve.

In acute infectious polyarthritis, the comparative sedimentation index is useful in the determination of the part played by the aspirated joint within the general process.

In monarticular arthritis, a high increase in the blood sedimentation and a low sedimentation rate in the synovial fluid indicate foci of infection outside of the joint as responsible for the increase in the sedimentation in the blood.

A simultaneous determination of the sedimentation and the viscosity is helpful in differentiating the type of involvement of the joint.

Noninflammatory fluids with a low protein content have a low comparative sedimentation index and a low viscosity. This is the case in transudates. On the other hand, fluids with a high content of mucin show a low comparative sedimentation index but a high viscosity.

The differentiation of infectious from degenerative types of chronic arthritis by the sedimentation of the blood alone is not possible. The nature of the underlying process can, however, be more accurately discovered by the comparative sedimentation and the viscosity of the effusion.

NOTE.—This method of comparative sedimentation was also used with other body fluids (pleural, pericardial and ascitic effusions). Four cubic centimeters of citrated blood is sufficient, as these fluids have a low viscosity. Two cubic centimeters is centrifugated, and the plasma is replaced by an equal volume of the citrated fluid to be examined. The tests are set up in the standard pipets for the Westergreen method. The findings will be reported elsewhere.

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CLINICAL SIGNIFICANCE OF ELECTROCARDIOGRAMS WITH LARGE Q WAVES IN LEAD III

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The occurrence of a large Q wave in lead III of the electrocardiogram in certain cardiac conditions has been noted recently by some observers.

Parkinson and Bedford[1] noted its presence in 9 of 29 patients (31 per cent) with a coronary thrombosis. In a series of 200 cases of heart disease of various types, Pardee[2] found 30 patients with the anginal syndrome. Of these, 8, or 27 per cent, were found to have a large Q wave in lead III. In the other 170 cases he found only 6 such records, or 3.5 per cent.

In reviewing the records of 277 normal hearts from other clinics, he found only 2 with large Q waves in lead III. He believes that this finding is closely associated with pathologic changes that involve coronary narrowing, and that the larger the Q wave in relation to the voltage of Q-R-S, the closer is this association.

Willius[3] reviewed approximately 70,000 electrocardiographic records at the Mayo Clinic and found 300 tracings which showed large Q waves in lead III. He stated, however, that this does not represent an accurate ratio of the incidence, owing to the fact that many tracings that previously had been considered to be essentially normal had been destroyed, and that it is possible that among these were some with large Q waves in lead III.

The majority (268, or 89.3 per cent) of the 300 records showing this sign were found in patients who had one of the following conditions: hypertensive heart disease, the anginal syndrome, hypertensive heart disease accompanied by the anginal syndrome, or arteriosclerotic

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From the Cardiac section of the United States Veterans' Hospital 106.

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1. Parkinson, J., and Bedford, D. E.: Successive Changes in the Electrocardiogram after Cardiac Infarction (Coronary Thrombosis), Heart **14**:195, 1928.

2. Pardee, H. E. B.: The Significance of an Electrocardiogram with a Large Q Wave in Lead III, Arch. Int. Med. **46**:470 (Sept.) 1930.

3. Willius, F. A.: Occurrence and Significance of Electrocardiograms Displaying Large Q Waves in Lead III, Am. Heart J. **6**:723, 1931.

heart disease not accompanied by the anginal syndrome or hypertension. He found only 3 cases (1 per cent) in which the heart was apparently normal.

Willius [3] believes that the occurrence of the large Q wave in lead III is associated with disorders in which there is a predominant strain on the left ventricle.

The present investigation is based on a study of 4,885 electrocardiograms of patients at the cardiac clinic of the United States Veterans' Hospital at Minneapolis. Eighty-six tracings, or 1.8 per cent of the entire group, were found which showed a large Q wave in lead III. The criteria set down by Pardee [2] were strictly adhered to in the selection of these records, namely: 1. The excursion of the Q wave in lead III must be more than 25 per cent of the greatest excursion

TABLE 1.—*Correlation of Large Q Waves in Lead III with Clinical Conditions in 86 Cases*

Clinical Diagnosis	Cases	Per Cent
Coronary disease with anginal syndrome	12	14.0
Hypertension	33	38.8
Hypertension with myocardial involvement	8	9.3
Aortic insufficiency	2	2.3
Mitral stenosis	1	1.2
Ascites	2	2.3
Gas distention	1	1.2
Cardiac hypertrophy	2	2.3
Pericardial adhesions	1	1.2
Nephrosis	1	1.2
Myocardial insufficiency	3	3.4
Normal heart	20	23.2
	86	100.0

of the Q-R-S complex in any lead. 2. They must show left axis deviation of Q-R-S with R_1 greater than R_2 or a normal direction of the axis of Q-R-S with R_2 larger than either R_1 or R_3. 3. All records must show in lead III an initial downward deflection (Q) followed by a definite upward deflection (R) without an S wave. 4. Records with a downward deflection in lead III followed by an upward deflection and then another downward deflection, resembling somewhat the shape of the letter W, and also records that had somewhat the shape of a letter M were excluded.

The distribution of cases showing the large Q wave in lead III and the classification of the clinical diagnoses are shown in table 1.

It will be seen that the greatest incidence of the characteristic electrocardiographic changes occurred in the group with hypertensive heart disease, 33 of the 86 cases (38.8 per cent) being obtained in this type. This compares favorably with Willius' [3] series, in which 40 per cent were found among the patients with hypertensive heart disease. Coronary

disease with angina pectoris was found in 12 cases (14 per cent). This is a smaller percentage than in Willius'[3] series, which shows 25.3 per cent with the anginal syndrome, and Pardee's[2] series which shows 62.8 per cent of the cases with the anginal syndrome. This may be accounted for by the fact that the present study was made on a group of men, the majority of whom were in the fourth and fifth decade of life, while the other studies included persons of all ages and perhaps many more patients in the later decades.

The other clinical cardiac conditions found compare favorably in distribution with both Willius'[3] and Pardee's[2] series, except for the percentage of normal hearts found.

It is significant that in the present study, a large Q wave in lead III was found in 20 patients with normal hearts, or 23.2 per cent of the entire group of 86 cases, while in Pardee's[2] series no such cases were found, and in Willius'[3] series only 3 cases (1 per cent) were found in normal hearts. In the composite group of electrocardiograms made from 977 normal persons in their control series, only two cases (0.2 per cent) with this characteristic electrocardiographic sign were found.

The finding of so large a percentage of normal hearts in my series led to the study of other factors which might be involved in the production of the large Q wave in lead III besides those given by Pardee[2] and Willius.[3] The position of the heart within the thoracic cavity, the size of the heart and the electrical axis were investigated in each case of this group and compared with a control group of an approximately equal number of cases with the same clinical diagnosis and with electrocardiograms having either a small Q wave in lead III or no Q wave at all. The findings are recorded in tables 2 to 6.

A significant difference in the angle of inclination of the heart was noted between the roentgenograms of the Q wave series and those of the control series. The angle of inclination of the heart in the Q wave series varied from 20 to 40 degrees, the average for the entire group being 29.6 degrees. One patient with mitral stenosis showed a cardiac angle of 44 degrees. In the control series the angle of inclination of the heart was 40 degrees or over in the majority of the cases, the average for the entire group being 42.9 degrees. There is a difference of over 13 degrees in the relative position of the heart between the Q wave series and the control series. The heart tends to lie in a more horizontal position in the chest cavity in the group showing large Q waves in lead III. This variation is practically constant in all of the clinical conditions studied and also in the normal hearts. It must be considered, therefore, a significant factor in the causation of large Q waves in lead III.

TABLE 2.—*Hypertension*

Q Wave Series					Control Series			
Name	Cardio-thoracic Ratio (X-Ray) per Cent	Cardiac Angle (X-Ray) Degrees	Electrical Axis, Degrees	Q Wave (Percentage of Greatest R Deflection)	Name	Cardio-thoracic Ratio (X-Ray) per Cent	Cardiac Angle (X-Ray) Degrees	Electrical Axis, Degrees
LA	39	32	+67	33	HAP	41	47	+62
JMA	46	28	+46	83	NKR	43	46	+59
WAA	45	36	+55	45	PPM	40	42	+52
GB	44	30	+49	75	EJB	42	36	+41
AB	48	30	+58	62	JHF	43	45	+77
EEC	50	36	+59	28	LdeS	45	37	+64
AC	55	28	+51	46	FGJ	49	46	+78
VC	46	35	+47	33	WBJ	45	45	+84
ERC	42	42	+49	50	HL	45	40	+12
WD	46	33	+49	50	JAM	50	45	+69
JdeM	45	34	+50	27	JKL	49	39	+52
WAF	41	30	+76	57	HJS	45	43	+55
JF	49	31	+55	50	EPS	47	40	+52
VF	48	32	+50	33	CS	46	45	+48
JF	46	35	+58	50	JB	41	54	+73
CLH	46	31	+49	40	FDC	43	45	+67
EH	52	27	+67	33	TPY	34	56	+69
EMI	48	40	+47	66	RGW	45	44	+73
JJ	48	24	+41	33	ALS	46	46	+43
BLK	44	26	+58	47	PS	42	43	+24
OM	48	29	+45	30	WHS	44	37	+16
MMcM	48	27	+44	25	IS	41	36	−30
DMcC	47	29	+45	45	FJV	45	43	+65
SGM	46	33	+55	25	TFR	44	42	+40
FWP	43	30	+45	27	GA	41	40	+48
RCP	46	30	+69	57	SS	48	41	+55
TR	52	25	+44	25	DL	47	45	+49
JS	57	23	+52	40	DW	46	44	+46
GS	52	31	+51	25	AH	40	47	+69
MBS	51	33	+53	37	CE	68	39	+11
WAS	47	33	+52	33	AB	43	42	+11
WT	52	28	+51	31	AR	43	49	+55
					CHH	50	40	−16

TABLE 3.—*Hypertension with Myocardial Involvement*

Q Wave Series					Control Series			
Name	Cardio-thoracic Ratio (X-Ray) per Cent	Cardiac Angle (X-Ray) Degrees	Electrical Axis, Degrees	Q Wave (Percentage of Greatest R Deflection)	Name	Cardio-thoracic Ratio (X-Ray) per Cent	Cardiac Angle (X-Ray) Degrees	Electrical Axis, Degrees
CC	50	32	+50	62	TTH	45	44	−50
JF	49	31	+55	55	EER	50	38	+73
JRG	55	26	+38	25	LL	50	36	−28
GJ	55	30	+49	76	HB	63	43	−27
NK	43	28	+46	42	HHF	52	45	+54
CDM	43	27	+55	55	JGH	55	40	+14
FE	48	25	+60	40				
WS	42	28	+50	46				

TABLE 4.—*Miscellaneous*

Q Wave Series					Control Series			
Name	Cardio-thoracic Ratio (X-Ray) per Cent	Cardiac Angle (X-Ray) Degrees	Electrical Axis, Degrees	Q Wave (Percentage of Greatest R Deflection)	Name	Cardio-thoracic Ratio (X-Ray) per Cent	Cardiac Angle (X-Ray) Degrees	Electrical Axis, Degrees
HA	57	27	+79	33	ES	45	43	+64
WK	46	35	+68	47	JD	48	45	+72
ON	40	44	+55	40	EJS	52	42	— 9
HK	47	27	+45	62	EM	42	46	+85
JS	53	20	+50	33	MAP	45	40	+86
CES	51	25	+44	50	MS	45	49	+48
FY	50	32	+80	33				
WD	48	33	+47	33				
JE	43	36	+62	44				

TABLE 5.—*Normal Heart*

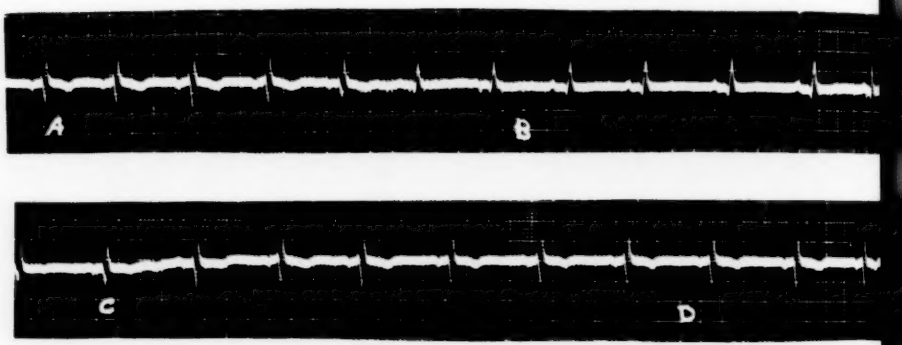
Q Wave Series					Control Series			
Name	Cardio-thoracic Ratio (X-Ray) per Cent	Cardiac Angle (X-Ray) Degrees	Electrical Axis, Degrees	Q Wave (Percentage of Greatest R Deflection)	Name	Cardio-thoracic Ratio (X-Ray) per Cent	Cardiac Angle (X-Ray) Degrees	Electrical Axis, Degrees
CA	30	35	+63	33	JKS	42	43	+40
LMB	50	25	+78	50	JMJ	45	42	+54
MB	50	32	+47	37	AWK	45	36	+85
FC	47	30	+44	50	FJK	46	49	+65
TD	46	24	+50	43	WY	44	55	+38
JED	42	25	+41	39	JN	50	38	+58
LJF	50	30	+42	38	HH	43	50	+72
HH	52	31	+42	40	BK	39	46	+71
LJ	45	37	+46	30	WK	41	52	+84
HAK	48	26	+51	30	AN	40	45	+30
GL	45	25	+50	30	JJW	48	41	+40
EL	45	30	+75	45	WJM	43	45	+54
HM	44	31	+46	40	EGP	48	50	+65
EO	50	27	+50	33	RB	41	49	+62
PS	47	27	+62	27	EA	48	40	+50
OS	54	20	+54	50	HES	48	43	+64
ET	45	35	+64	27	TI	44	43	+38
EW	45	33	+55	30	MB	47	40	+47
EJW	47	35	+56	37	ED	40	53	+82
RO	51	25	+54	83	HAM	38	45	+69
					MS	50	45	+43
					CB	48	40	+55
					AAH	45	43	+58

TABLE 6.—*Comparison of the Average Angle of Inclination of the Heart in Various Clinical Conditions in the Q Wave Series and in the Control Series*

Clinical Diagnosis	Coronary Disease	Hyper-tension	Hyperten-sion with Myocardial Involvement	Miscel-laneous	Normal Hearts	Average
Q wave series	28.9	30.9	28.4	31.0	29.1	29.6
Control series	....	43.3	41.0	42.7	44.9	42.9

That the form of the normal electrocardiogram may be influenced by the position of the heart is well known.[4] It has been frequently observed that short, stout persons in whom the heart is transversely placed show electrocardiograms indicative of left ventricular preponderance.

Cohn [5] has shown that by shifting the location of the leads, or rather by changing the angle of the heart in respect to the leads, from 46 to 6 degrees, a change in the form of the electrocardiogram takes place, and that this form resembles that associated with left ventricular preponderance. That changing the position of the heart in a normal person by deep inspiration and deep expiration affects the Q wave also is shown in the accompanying figure. It will be seen that on deep inspiration, when the heart tends to assume a vertical



Electrocardiogram showing the effect of change of the position of the heart due to respiration on the Q wave in Lead III. *A*, beginning of deep inspiration; *B*, holding the breath in deep inspiration; *C*, beginning of expiration, and *D*, holding the breath in complete expiration.

position, the Q wave is practically absent, while on complete expiration, when the heart is pushed up by the diaphragm and tends to assume a more horizontal position, a large Q wave is present. It is also noted that the size of the Q wave increases inversely as the angle of the heart decreases with the change in respiration. Pardee [2] has made similar observations in his study. He also found that a record taken of

4. Einthoven, W.; Fahr, G., and de Wart, A.: Ueber die Richtung und die manifest Grösse der Potentialschwankungen im menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, Arch. f. d. ges. Physiol. **150**:275, 1913.

5. Cohn, Alfred E., and Raisbeck, M. J.: An Investigation of the Relation of the Position of the Heart to the Electrocardiogram, Heart **9**:311, 1922.

a woman during the eighth month of pregnancy shows a large Q wave in lead III, while one taken after delivery shows no Q wave. Pardee stated that a high position of the diaphragm may be a contributory factor in the production of large Q waves in lead III of the electrocardiogram.

Three cases of my series show distinctively the effect of the shifting of the position of the heart due to mechanical causes in the production of Q waves in lead III. In two of the cases ascites was the cause, and in the third marked distention of the abdomen due to gas was responsible for the change of position of the heart.

That there may be other factors involved in the production of the large Q waves is not denied. Purks [6] recently reported his electrocardiographic findings following the ligation of the descending branch of the left coronary artery in man. He noted that the Q wave increased in size after ligation, and exceeded 25 per cent of the greatest R from

TABLE 7.—*Association of Negative T Waves with Large Q Waves in Lead III*

T Wave Negativity	Pardee Series		Willius Series		Ziskin Series	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Lead I	1	2.5	28	9.3	7	8.1
Lead I and II	14	9.0	20	6.6	2	2.3
Lead II and III	1	25.0	27	9.0	5	5.8
Lead I, II and III	0	0.0	11	3.7	3	3.4
Total	16	37.2	86	28.6	17	19.6

the fourth to the sixth days, the maximum increase occurring on the fifth day.

A study of the size of the Q waves in the present series shows that the largest Q waves occurred in the cases of coronary disease, 65 per cent of the group showing Q waves larger than 50 per cent of the greatest R. In the group with hypertension together with myocardial involvement, 50 per cent showed a Q wave over 50 per cent of the greatest R; in the group with hypertension alone, 30 per cent showed this characteristic, while in the group with normal hearts 20 per cent showed the Q wave over 50 per cent of the greatest R.

The significance of T wave negativity was compared with the observations of Willius [3] and Pardee,[2] and the results are shown in table 7.

The occurrence of T wave negativity according to leads in my series compares more favorably with that of Willius [3] than that of Pardee.[2] It appears, therefore, that damage to the left ventricle, as a

6. Purks, W. K.: Electrocardiographic Findings Following Ligation of the Descending Branch of the Left Coronary Artery in Man, Am. Heart J. **7**:101, 1931.

result of coronary disease, with or without infarction, or of hypertension, may be an associated factor in the production of large Q waves in lead III of the electrocardiogram.

SUMMARY

In 86 cases in which there were large Q waves in lead III, conforming to the criteria laid down by Pardee,[2] 20, or 23.2 per cent, were found in patients with normal hearts and 33, or 38 per cent, were found in patients with hypertension and with no other sign of cardiac involvement, while 12, or 14 per cent, were found in patients with coronary disease and 8, or 9.3 per cent, in patients with hypertension together with myocardial involvement.

A comparison with a control series of an equal number of cases shows that the relative position of the heart within the thoracic cavity is the most common factor associated with the finding of large Q waves. The average angle of inclination of the heart in the group with large Q waves in lead III was 29.6 degrees, while in the control series it was 42.9 degrees, a variation of 13.3 degrees.

This variation was constant in all the clinical conditions and also in the normal hearts.

The effect of change of position of the heart on the Q wave in lead III as a result of respiration is shown in a record made during inspiration and expiration.

The predominance of Q waves over 50 per cent of the greatest R, in the groups with coronary disease and in those with hypertension accompanied by myocardial involvement, the greater distribution of T wave negativity in leads I and II of the electrocardiogram and the experimental evidence introduced showing that ligation of the descending branch of the left coronary artery increases the size of the Q wave in lead III would tend to show that damage to the myocardium of the left ventricle as a result of these conditions is an associated factor in the production of a large Q wave in lead III of the electrocardiogram.

PRODUCTION OF NONFATAL VASCULAR SCLEROSIS IN RABBITS BY MEANS OF VIOSTEROL (IRRADIATED ERGOSTEROL)

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Since the observation that certain substances acquire antirachitic properties following exposure to ultraviolet rays,[1] great interest has centered on the artificial production of vitamin D and on its relationship to the diseases concerned with calcium metabolism. Soon after the initial discoveries, it was established [2] by a series of brilliant investigations that the specific substance activated by irradiation was ergosterol. The efficacy of viosterol (irradiated ergosterol) in the treatment of rickets and osteomalacia was quickly established. In addition, workers [3] studied the effects of this material on normal laboratory animals. They demonstrated that an elevation of the blood calcium occurred and that calcium was deposited in the arterial walls, especially the aorta, and in the muscle of the heart, the wall of the

From the Pathological Laboratory of the Boston City Hospital.

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stomach, the lungs and the kidneys. In still other experiments [4] it was shown that even more widespread calcification occurred, and that the animals frequently had a retention of nitrogenous products in their blood before death.

There has been fairly general agreement that the deforming, sclerotic changes of the aorta were most extensive in the ascending and transverse portions, and that the bronchial cartilages and kidneys contained marked deposits of calcium. In general, the previous workers confined their observations to the study of the terminal changes in the tissues, after the animals died from poisoning with viosterol. However, some attempted, by killing the animals during the course of medication, to demonstrate the progression of the lesions. Schiff [5] observed a period of partial recovery in some of her animals between the administration of the last dose of viosterol and the subsequent spontaneous death.

In view of the specific manner in which viosterol produces severe lesions in the organs of such great clinical importance as the aorta, lungs and kidneys, it seemed of especial importance to damage extensively these structures without causing the death of the animal.

The present paper deals with the production of such lesions in rabbits, without causing their death. Also the residual changes after the animals were killed (three and one-third months later) were studied.

MATERIALS AND METHODS

The four young rabbits used averaged 1,600 Gm. in weight and were fed on the usual laboratory diet. A preparation of viosterol, "10,000 D,[6]" having ten thousand times the antirachitic potency of cod liver oil was administered by stomach tube, in individual doses of from 5 to 7 cc. at intervals of from four to five days. At times the animals were freed from medication for one or two weeks ("rests," while recovering from toxic doses). The total duration of the period of administration (including "rests") ranged from forty to seventy days. The animals were then allowed to recover and later were killed, from ninety-seven to one hundred and two days after the final dose of viosterol was given. Determinations of the blood urea were made at the beginning of the experiment and about one week after the cessation of medication.

A series of three control animals received the nonactive solvent oil that was used in the preparation of the viosterol employed.

Soon after the gross examination of the organs, sections were fixed in an alcohol-formaldehyde mixture (9 parts of 95 per cent alcohol to 1 part of 40 per cent formaldehyde), in 10 per cent formaldehyde, in 95 per cent alcohol and in

4. Spies, T. D.: The Calcification of Tubercles by Means of Irradiated Ergosterol, Am. J. Path. **6**:337, 1930. Spies, T. D., and Glover, E. C.: Renal Lesions with Retention of Nitrogenous Products Produced by Massive Doses of Irradiated Ergosterol, ibid. **6**:485, 1930.

5. Schiff, A.: Changes Produced in Blood Vessels by Vigantol, Virchows Arch. f. path. Anat. **278**:62, 1930.

6. This preparation was furnished through the courtesy of Mead Johnson & Company.

Zenker's fluid. Some of the tissues fixed in formaldehyde were embedded in celloidin and stained with either hematoxylin and eosin or by the silver method of von Kossa. The tissues fixed in Zenker's fluid were embedded in paraffin and stained with eosin-methylene blue (methylthionine chloride, U. S. P.) and in some instances with Weigert's elastic tissue stain. The deposits of calcium were identified by their solubility in acid and by the following histologic criteria, using principally formaldehyde-fixed material: (1) When stained with hematoxylin and eosin, the precipitated calcium appeared as a dark blue, coarsely granular material; (2) after treatment with silver nitrate solution and counter-staining with a 0.5 per cent solution of basic fuchsin, the deposits assumed a deep brownish-black color.

OBSERVATIONS

A temporary loss of the rabbit's body weight occurred soon after the administration of viosterol was begun. Cachexia, loss of appetite and sometimes diarrhea developed as the administration was continued. Several times the animals appeared so near death that the administration of the substance was discontinued for from seven to fourteen days. Soon after receiving the final dose of viosterol the animals began to eat better and gain weight, and they still had normal readings for blood urea. A few weeks later they appeared in splendid health and continued to gain weight until they were killed.

The control animals gained weight and appeared healthy throughout the experiment.

PATHOLOGIC DESCRIPTIONS

While the organs of all animals were examined grossly and microscopically, only the changes in the aorta, lungs and kidneys will be described in this report.

Aortas.—The aortas from the four animals that received viosterol appeared as thick-walled, rigid tubes. The sclerotic process extended from the aortic cusps to the iliac bifurcation. However, the ascending aorta and the tranverse arch were especially involved. Here the vessels showed aneurysmal dilatation (often twice the diameter of normal). They were hard (calcified), irregular in contour and tortuous. The remaining portion of the aortas was affected in the same manner, but to a progressively less degree as the examination approached the iliac bifurcation. It was obvious from the external appearance that the deformity of the walls was caused by innumerable areas of varying sizes and shapes in the walls, which often bulged out from the lumina. In a few instances the lesions protruded inward so as to reduce the caliber of the vessels. The intimal surface was occupied by the same type of closely situated deforming areas. They ranged from 0.6 to 0.2 cm. across, and their contiguous borders were separated by thin partitions, which were usually seen to lie transversely to the axis of the aorta. The lining was smooth, free from ulcerations and firm. When

a cross-section of the aorta was taken, the media was found to contain a grayish-white material (calcium).

The aortas of the control animals were normal.

Lungs.—The lungs from the animals receiving viosterol were of normal size, shape and color. The trachea and larger bronchi were thickened and abnormally rigid. They were free from exudate. When these were sectioned, a grayish-white line could often be seen within their walls. The parenchyma and pulmonary vessels appeared normal.

The lungs from the control animals were normal.

Kidneys.—The kidneys from the animals that received viosterol were normal in size, shape and consistence. However, after sectioning, innumerable small, but easily visible, grayish-brown lesions (calcium) could be seen throughout the cortex. Similar deposits were grouped in the medulla to form a thin strip which ran parallel to the curve of the cortex, 0.2 cm. medial to its inner border. In all instances the cortex and medulla were well demarcated and of normal thickness.

The capsule of each kidney was thin; it stripped with ease and left a smooth, glistening surface. Mild sclerosis was observed in a few of the large branches of the renal arteries. The pelves appeared normal.

The kidneys from the three control animals were normal.

MICROSCOPIC DESCRIPTION (FORMALDEHYDE FIXATION)

Aortas.—The aortas from all animals that had received viosterol were severely deformed. Many irregularly sized and shaped areas of hyalinization and calcification were distributed through the media. The medial changes were usually most marked in the region of the internal elastic lamina. Almost the entire wall was involved in the more advanced lesions, but in the less involved regions the change was limited to small portions of the internal elastic lamina and sometimes to the adjacent portions of the media. In the latter areas, the adjacent hyalinized and calcified foci had not fused to form an encircling layer around the lumen. Oftentimes the adjacent edges of these lesions were separated by normal-appearing tissue. The elastic tissue was usually severely damaged. At times the fibers appeared hyalinized, but in other instances they were irregular in size, shape and distribution. In the still more advanced lesions, the elastic tissue could not be identified.

It is noteworthy that the aortas in this series were slightly less involved than those previously studied.[4] It is worthy of emphasis that the larger lesions in the aortas of the present series contained more necrotic cellular débris and less visible calcium than comparable lesions from the aortas of the animals studied previously. It seemed as though

the lesions of the present series of animals had a relative increase in the degenerative process and a relative lack of the extensive deposits of calcium. Does this mean that the affected cells go on to degeneration and that some of the deposited calcium has been reabsorbed by the animals?

The aortas from all control animals were normal.

Lungs.—The trachea and bronchial cartilages taken from the animals that had received viosterol were heavily calcified. In many instances the area of calcium deposition within the trachea was as large as 0.1 cm. A thin concentric area of hyalinization and calcification was situated just beneath the bronchial epithelium. The tracheal

Fig. 1.—Photomicrograph of a slightly involved area of the aorta. Note the deposit of hyaline material and calcium in a layer. The adjacent tissue appears normal; × 117.

and bronchial epithelium was frequently calcified, and at times the alveolar epithelium contained deposits of calcium. Calcification was absent within the walls of the vessels.

The trachea and lungs of the control animals were normal.

Kidneys.—The kidneys from all animals that had received viosterol were conspicuously involved. The arteries, arteriole, tubules and glomerular capsules were prominently hyalinized and calcified. In general, these lesions were similar to, but less extensive than, the lesions previously described.[4] It is interesting that the renal lesions in the animals of the present experiment contain less visible deposited calcium than comparable lesions in the renal tissues described in the former experiments. On the other hand, the hyalinization process appeared more prominent in some of the comparable lesions of the

present series than in the former experiments. The hyalinization and calcification were so intimately related that the paucity of the deposits of calcium would cause an apparent increase in the amount of hyaline formation. It is also noteworthy that the deposits of calcium are strikingly fewer in the tubules of the kidneys of this series. Could the apparent decrease in the prominence of deposits of calcium mean that the calcium has in part been excreted by the animals?

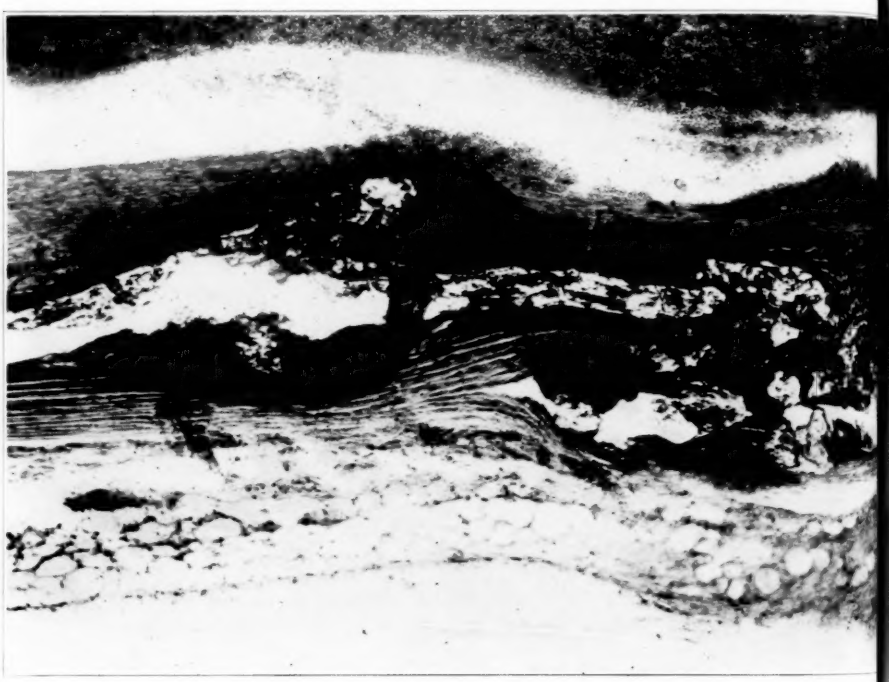

Fig. 2.—Photomicrograph of a severely involved area of the aorta. Note the splitting of the wall and the presence of hyalinized material and calcium; reduced from a magnification of × 117.

ZENKER'S FIXATION

Calcification was absent in all tissues fixed in Zenker's fluid because the acetic acid had removed the precipitated calcium from the tissues. Hyalinization of the involved sites was extensive. The sites of calcification in the aorta, lungs and kidneys now appeared as poorly stained, faintly blue areas. These areas were hyalinized, and in many instances cellular detail was obscured, but in others vacuolated cells and pyknotic nuclei were observed. In some regions polymorphonuclear and endothelial leukocytes were found in the fused masses of necrotic material.

COMMENT

It has been shown in the experiments reported here that the administration of repeated, massive doses of viosterol produced a severe and persistent sclerosis of the aorta and renal vessels. This phenomenon was associated with calcium deposition within the parenchyma of the lungs and kidneys. It is worthy of emphasis that soon after the final dose of viosterol was administered all animals regained their appetites and body weight. They continued to have normal renal function. At the termination of the experiment, they appeared in the best of health.

In general, the vascular process was one of extensive sclerosis with hyalinization and calcification of the media. The pulmonary changes consisted of calcification of the trachea, bronchial cartilages and, at times, bronchial and alveolar epithelium. Deposits of calcium were absent in the pulmonary vessels. The renal arteries, arterioles, tubules and glomerular capsules were hyalinized and calcified.

The lesions in this series of experimental animals were slightly less prominent than the lesions of the animals that were allowed to die from poisoning with viosterol. However, they are considerably more extensive than the lesions produced by some other workers who allowed the animals to die from massive doses of viosterol. The lesions studied, three and a third months after their production, were extreme, and I think that they represent about the maximal degree of involvement compatible with the animal's return to apparent health.

In many lesions of the present series of experimental animals the apparent proportion of hyalinized tissue to microscopically visible calcium was greater than in comparable lesions of the previous experiments, thus suggesting that some of the calcium had been reabsorbed during the three or four months after cessation of medication. Naturally, the vascular deformity would be expected to remain despite any tendency of calcium reabsorption. The vascular sclerosis produced in these experiments is not the result of spontaneous atherosclerosis, which sometimes occurs in older rabbits. Also, the experimental lesions do not in any way resemble the changes found in the aortas of rabbits following the administration of cholesterol or unirradiated ergosterol. It seems that this study gives a method of producing permanent severe sclerosis of the aorta and renal vessels.

SUMMARY AND CONCLUSIONS

1. It has been shown in the experiments reported here that severe and persistent damage can be produced in such vital organs as the aorta, lungs and kidneys without causing death to the animals by repeated administration of toxic doses of viosterol.

2. A comparative study of the residual lesions in this experiment with similar lesions in previous work suggests that the animal was in time able to reabsorb some of the deposited calcium.

TRANSIENT VENTRICULAR FIBRILLATION

THE CLINICAL AND ELECTROCARDIOGRAPHIC MANIFESTATIONS OF THE SYNCOPAL SEIZURES IN A PATIENT WITH AURICULOVENTRICULAR DISSOCIATION

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AND
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In a recent communication [1] it was pointed out that periods of unconsciousness in patients with auriculoventricular dissociation are associated with transient seizures of ventricular fibrillation much more commonly than has been suspected hitherto. Attention was called to the fact that a clinical diagnosis of transient ventricular fibrillation may be suspected in such patients if preceding a period of unconsciousness the heart rate has been noted to increase above that of the usual basic rate.

Within the past few months we have been able to confirm these findings in another woman with complete auriculoventricular dissociation and transient syncopal seizures in whom some of the premonitory periods preceding the attacks of unconsciousness resembled those observed in our previous case. However, on careful study of the electrocardiograms obtained at the same time that the patient was observed clinically, another type of cardiac mechanism was found to precede the periods of unconsciousness.

In view of the fact that the alterations in rhythm lend themselves to a clinical analysis, it becomes increasingly important to appreciate them, since hitherto little attention has been paid to the various mechanisms responsible for syncopal seizures in patients with heart block.

REPORT OF CASE

History.—M. G., a Jewish woman, aged 65, was admitted to the Montefiore Hospital on Sept. 9, 1931. Her chief complaints on admission were recurrent seizures of unconsciousness accompanied at times by convulsions and attacks of precordial pain. These symptoms were of six months' duration.

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1. Schwartz, S. P.: Transient Ventricular Fibrillation: A Study of the Electrocardiograms Obtained from a Patient with Auriculoventricular Dissociation and Recurrent Syncopal Attack, Arch. Int. Med. **49**:282 (Feb.) 1932.

The patient had been well and up and about until October, 1930, when she began to complain for the first time of precordial pains, which usually came on suddenly without any warning. They were sharp, localized to the midsternal region and of short duration. They bore no relationship to meals and exertion. However, because of the accompanying symptoms of sweating and "pallor" she decided to rest in bed.

In April, 1931, the patient began to suffer from periodic attacks of unconsciousness lasting for several minutes at a time and associated with incontinence of both feces and urine. Members of her family who saw her in these attacks described them as coming on suddenly without any warning. The patient had been seen during a seizure to shut her eyes, become very pale and then intensely blue and breathe stertorously. Occasionally convulsive seizures of all extremities would end an attack, and following such episodes the patient would awaken and scream loudly, not knowing what had happened to her in the previous few minutes.

Occasionally the convulsive seizures were followed by a semicomatose period lasting as long as five hours, with the patient only gradually regaining orientation. During such times her speech would be unintelligible.

In June, 1931, she entered the Lebanon Hospital, where it was noted that her pulse rate was slow, averaging between 28 and 38 beats per minute. The recurring attacks of unconsciousness were diagnosed as Stokes-Adams seizures in a patient with a slow heart rate. On the assumption that they were due to standstill of the ventricles, the patient was given barium chloride in doses of 30 mg. three times a day and epinephrine hydrochloride in doses of 0.5 cc. of the 1 : 1,000 solution sometimes three and sometimes four times a day intramuscularly.

Instead of improving under this form of therapy, she became worse. Indeed, in reviewing the number of syncopal seizures during her stay at the Lebanon Hospital, it was almost impossible to believe that she had had so many attacks in a single day. Therapy was continued until the day of her transfer to our institution.

Physical Examination.—Examination on admission to the Montefiore Hospital revealed an old woman lying comfortably in bed with only one pillow under her head. Her face had a peculiar yellow, grayish color. The superficial veins of the neck were moderately distended, but they did not show any auricular pulsations. The right carotid artery was thick and tortuous. The apical impulse of the heart was in the sixth intercostal space in the anterior axillary line. The heart sounds were of poor quality. They varied in intensity from beat to beat. The heart rate was between 32 and 50 beats per minute; it was irregular, with only about two thirds of the heart beats causing a pulse in the radial artery.

The blood pressure was 170 mm. of mercury systolic and 60 mm. of mercury diastolic.

The lungs showed moderate moisture at both bases posteriorly. The abdomen was lax and soft, and the edge of the liver was barely palpable. The lower extremities showed slight pitting edema.

Roentgen examination of the chest revealed moderate pulmonary congestion and marked dilatation of the cephalobrachial vessels.

The heart was placed horizontally and showed moderate general enlargement of the left ventricle. The arch of the aorta was elongated and dilated, and there were numerous calcific areas in it.

An electrocardiogram made on the day following admission showed complete auriculoventricular dissociation with a regular ventricular rate of 28 and a regular auricular rate of 66 beats per minute. The ventricular complexes were all of the upright form; they were supraventricular in type, and they varied in size from beat to beat.

The Wassermann reaction of the blood was negative.

The unusual history that this patient presented prompted us to place her, immediately after admission, under close supervision, and for the four months following her admission to the Montefiore Hospital she was seen and studied preceding, during and subsequent to several hundred attacks of unconsciousness. More than a hundred of these attacks were recorded electrocardiographically, and they all proved to be due to ventricular fibrillation. From the clinical correlations of these records we have been able to appreciate the variations in the heart rate and rhythm preceding and succeeding ventricular fibrillation.

THE NATURAL COURSE OF TRANSIENT VENTRICULAR FIBRILLATION

The natural course of the syncopal attacks due to transient ventricular fibrillation in the patient is unusual. The seizures were variable from day to day, and on the same day they varied from hour to hour. They showed no definite diurnal or nocturnal periodicity. They occurred as frequently during the patient's deep sleep as when she was awake. They had no relationship to meals, exertion or defecation. It was impossible to produce them by exercise. However, fright and emotional disturbances seemed to induce their appearance.

During the four months she has been under observation, she has not passed a single day without having at least one syncopal attack due to ventricular fibrillation. She has been seen in as many as two hundred and seven attacks of unconsciousness during a period of twenty-four hours, at the end of which time she did not present any physical findings different from those seen on the previous day when she had only a few minor seizures (table).

The attacks varied in duration from only a few seconds each to close to six minutes. The longer seizures were invariably accompanied by incontinence of either feces or urine. The average duration of these seizures was approximately forty-six seconds.

The shorter attacks did not influence the sensorium. The longer attacks, usually those lasting a few minutes at a time and coming in frequent succession, clouded the memory. Following such an experience the patient would speak unintelligently for several hours at a time, and frequently she would go into a semistuporous condition from which she could be easily aroused.

She did not complain of any precordial distress. Occasionally she was nauseated and frequently vomited during a seizure without her knowledge, for she was unconscious.

Only at one time did we note any tenderness over the hepatic region following a long series of these seizures, and on several occasions pitting edema of the legs was present. Even now her lungs are remarkably free from moisture.

In the periods preceding the attacks, the patient was not aware of any peculiar precordial sensations, nor did she experience any palpitations of the heart.

The Number of Syncopal Attacks Due to Ventricular Fibrillation Experienced by the Patient During a Period of Twenty-Four Hours, at a Time When the Attacks Were Unusually Frequent

Date and Time of Day	Duration, Seconds	Date and Time of Day	Duration, Seconds	Date and Time of Day	Duration, Seconds	Date and Time of Day	Duration, Seconds
10-30-31 p.m.		10-30-31 p.m.		10-30-31 p.m.		10-31-31 a.m.	
1:00	20	4:25	10	7:55	1	3:30	1
1:32	30	4:28	20	7:56	1	3:50	2
1:35	40	4:31	25	7:59	1	3:51	1
1:40	20	4:34	30	8:00	15	4:00	18
1:41	5	4:35	7	8:05	7	4:05	1
1:44	15	4:41	20	8:10	62	4:10	2
1:47	20	4:43	60	8:15	22	4:15	18
1:48	20	4:46	20	8:16	34	4:20	15
1:49	8	4:50	25	8:20	38	4:25	2
1:51	2	4:55	10	8:25	1	4:35	16
1:55	25	5:02	20	8:29	32	5:00	10
1:59	5	5:04	30	8:30	1	5:03	18
2:00	28	5:07	25	8:31	26	5:20	10
2:10	10	5:14	15	8:37	4	5:30	11
2:12	30	5:15	130	8:45	31	5:44	17
2:17	30	5:22	35	8:48	3	6:00	8
2:19	10	5:25	30	8:55	2	6:10	10
2:21	8	5:31	3	9:00	70	6:15	2
2:25	15	5:40	25	9:02	1	6:35	17
2:27	25	5:43	5	9:10	12	6:37	15
2:31	3	5:45	4	9:15	18	6:50	24
2:33	30	5:58	10	9:22	2	6:56	20
2:35	8	5:59	30	9:25	30	7:10	20
2:41	23	6:00	4	9:30	13	7:15	40
2:44	4	6:30	2	9:35	20	7:20	5
2:47	2	6:31	10	9:37	20	7:30	25
2:58	3	6:32	2	9:40	22	7:45	6
2:59	1	6:38	2	9:41	23	8:00	5
3:01	40	6:46	10	9:43	15	8:15	3
3:15	15	6:50	20	9:45	20	9:00	10
3:16	1	6:52	40	9:49	2	10:05	2
3:18	4	6:56	2	9:50	12	11:04	90
3:21	35	6:58	40	9:51	8	11:25	35
3:26	2	7:07	2	9:54	7	11:27	62
3:29	20	7:..	10	10:00	3	11:32	24
3:31	5	7:13	40	10:05	1	11:55	15
3:34	3	7:20	3	10:35	2	p.m.	
3:36	2	7:22	1	11:00	2	12:45	45
3:40	50	7:25	3	11:45	2	12:55	24
3:46	40	7:30	2	10-31-31		12:57	8
3:58	35	7:35	1	a.m.		1:07	20
4:00	35	7:37	1	12:10	1		
4:05	10	7:39	1	12:30	1		
4:09	35	7:40	1	1:50	2		
4:10	15	7:41	1	2:30	14		
4:16	4	7:45	6	2:31	2		
4:17	20	7:46	4	2:46	16		
4:20	10	7:48	1	3:00	21		
4:21	30	7:50	3	3:20	10		
4:24	25	7:51	1	3:25	27		

THE CLINICAL MANIFESTATIONS PRECEDING TRANSIENT SEIZURES OF VENTRICULAR FIBRILLATION

The stages preceding a period of transient ventricular fibrillation were extremely uniform as compared with those reported previously.[1] Obviously the premonitory periods with their changes in rhythm varied in duration preceding each attack, but their mode of onset was practically the same.

The basic ventricular rate preceding an attack averaged 28 beats per minute and was only slightly irregular (fig. 1 *A* and *B*),[2] but this irregularity could not be appreciated clinically. The auricular rate was 66 beats per minute. The auricular contractions could not be heard during the interventricular silences. However, on listening to the apical region at such times a definite change in the quality of the heart sounds

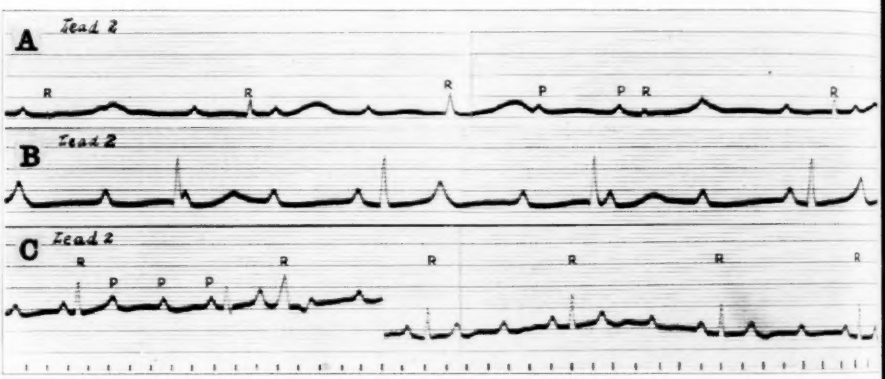

Fig. 1.—*A*, complete auriculoventricular dissociation. The basic ventricular rate is 28 beats per minute. The voltage of both the auricular and the ventricular complex is low. There is a variability in the size, shape and form of the main ventricular complexes from beat to beat. The auricular rate is 66 beats per minute. *B*, compare the voltage of the auricular and ventricular complexes with those in *A*. At such times the heart sounds were louder. *C*, partial heart block. The auricular rate is 120; the ventricular rate is 40.

could be made out. For a period of several minutes they could be heard distinctly and clearly, and then there would be a sudden transition to lower pitched and weaker sounds that were barely audible. At the same time the quality of the pulse also changed, suddenly becoming weaker and remaining so until the heart sounds increased in intensity again.

During the presence of the weak heart sounds, the electrocardiograms revealed low voltage of both the auricular and the ventricular

2. All of these studies were carried out with lead 2 only.

complex (fig. 1 *A*), whereas when the heart sounds were more audible, the voltages of these complexes were higher (fig. 1 *B*).

Occasionally the basic ventricular rate would increase suddenly from an average of 28 beats per minute to 40 beats. At such times the electrocardiogram invariably revealed partial heart block with a 3 to 1 rhythm, a ventricular rate of 40 and an auricular rate of 120 beats (fig. 1 *C*).[3] Syncopal seizures were not observed to follow any of these transitions from partial to complete heart block or vice versa, although we have obtained records of transient ventricular fibrillation during the presence of already established partial heart block. Frequently during the presence of both these regular rhythms, the Q-R-S complexes were variable from beat to beat in height as well as in duration, often assuming transitional changes from a dextrocardiogram to a levocardiogram and back again.

The ventricular rates during the presence of both partial and complete heart block were not influenced by exercise or sleep.

After several hours at one time and only several minutes at another, when the patient was feeling perfectly well, her ventricular rate, which averaged 30 beats per minute, would be suddenly disrupted by the appearance of alternate premature ventricular beats (fig. 2 *A*, *B* and *C*) which could be heard at the apex and distinctly felt at the pulse. Sometimes these premature beats would come in groups of 2 or more, all of them appearing to arise from different foci in the ventricles (fig. 2 *B*).

It was soon noted, however, at such times, when observations were made of the movements of the galvanometer string at the same time that the heart sounds and pulses were studied clinically, that when these extraventricular oscillations increased in frequency (fig. 2 *E* and fig. 3 *A*, *B* and C) only the first 4 beats following a basic ventricular complex could be heard at the apical region of the heart. These became progressively weaker in quality from beat to beat, so that all the oscillations appearing after the fifth one could be registered electrocardiographically, but could not be heard at the apical region of the heart.

With a little practice it was possible to learn these events in their order of sequence clinically so that we could predict the increase in the frequency of the ventricular oscillations and their duration by the appearance of "silent" pauses that interrupted the rhythm of the heart. As these pauses increased in number, the patient began to complain of dizziness, and she would shut her eyes momentarily.

3. This type of rhythm during the presence of complete auriculoventricular dissociation may be due to a fortuitous adaptation of the auricles to the ventricles. In this patient, however, the ventricles could be slowed at first by epinephrine at such times, indicating that the auriculoventricular pacemaker was under the influence of the vagus; consequently, the block was "partial."

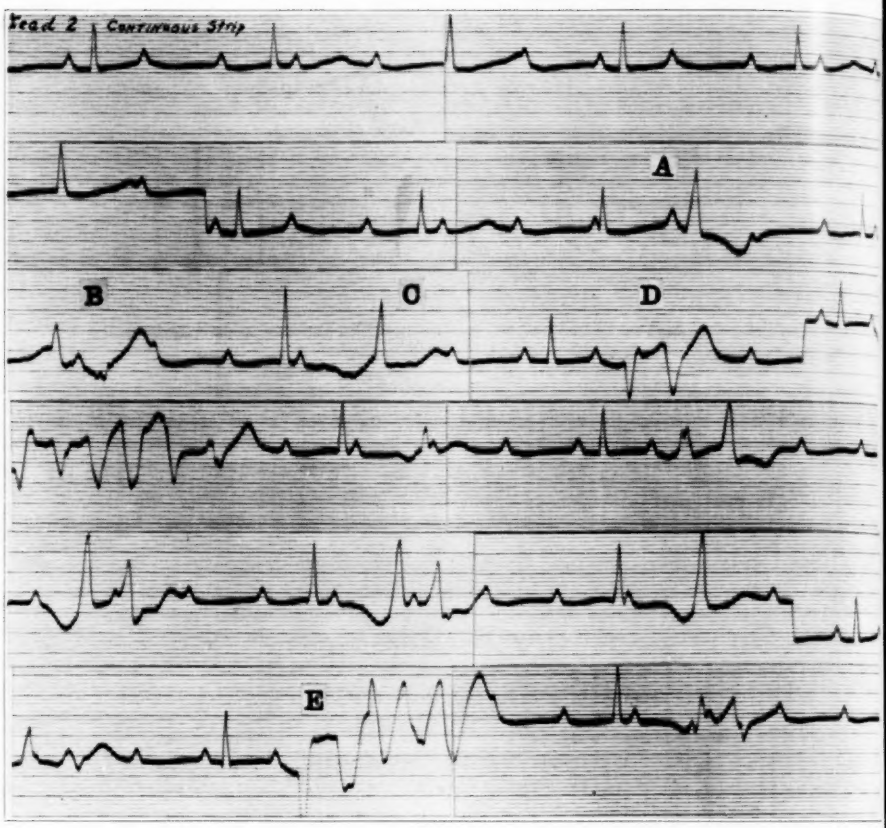

Fig. 2.—The premonitory period: Complete auriculoventricular dissociation. The basic ventricular rate is interrupted by the appearance of alternate premature ventricular beats (*A*, *B*, *C*) which are sometimes upright, but more usually are downward (*D*, *E*).

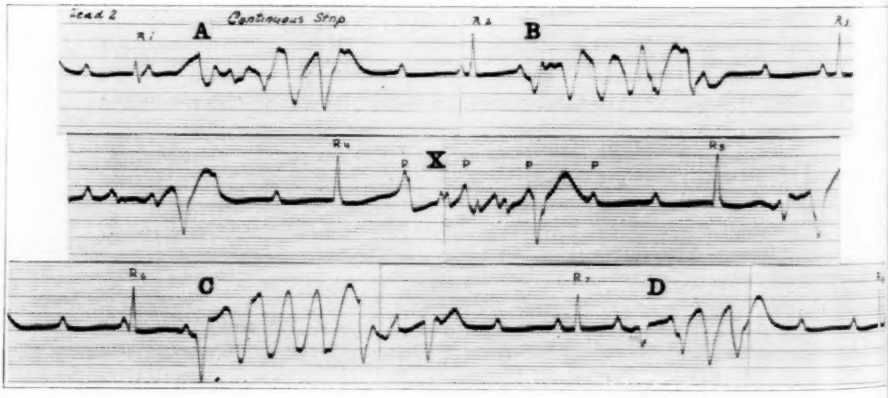

Fig. 3.—The premonitory period: Recurrent groups of aberrant ventricular oscillations interrupting the basic rhythm. At such times the patient showed alternate pallor and redness of the face. The auricular sequence is not disturbed (*X*).

With further practice it no longer became necessary to resort to auscultation of the heart to determine such pauses, because when the fingers became accustomed to the variations in the radial pulsations we could tell the presence of the ventricular oscillations. For, after a strong pulse a pause was found to follow successively several progressive shorter and weaker pulse beats. While clinically to the casual observer this premonitory period would appear as a reduction in the ventricular rate, actually there was a definite increase in it if we are to include the few heart sounds and palpable pulsations at the wrist that follow each basic ventricular complex, so that a heart rate of 30 beats would be increased rapidly to one of 50 when single premature beats appeared and to one of a higher rate when more appeared in rapid succession.

Sometimes the ventricular oscillations following the basic ventricular complexes appeared in recurrent groups (fig. 3 *A*, *B*, *C* and *D*), resulting in a disappearance of the pulse of from five to six seconds. After a while it was possible to associate this mechanism with an alternate pallor and flushing of the face, the pallor resulting from ineffectual peripheral circulation during the presence of the ventricular oscillations and the redness coming on with the marked forceful contraction of the ventricles associated electrocardiographically with the basic ventricular complex.

When the basic ventricular rhythm was interrupted by periods of ventricular fibrillation for a period longer than eight seconds, but for not more than twelve seconds, the patient's face assumed a deathly pallor, she shut her eyes and lapsed into momentary unconsciousness, to be suddenly awakened and startled as her face assumed a ruddy complexion, which coincided with a forceful beat of the heart.

Such short periods of unconsciousness of from eight to twelve seconds would invariably predicate and herald a typical major attack of syncope. Even during these shorter syncopal accidents (fig. 4 *A* and fig. 5 *A* and *B*) the patient was incontinent of feces and of urine.

THE ALTERATIONS IN THE ELECTROCARDIOGRAM PRECEDING TRANSIENT VENTRICULAR FIBRILLATION

The initial ventricular complexes of the recurring groups of ventricular oscillations that begin to disrupt the basic rhythm so as to increase the ventricular rate and indicate the approach of a syncopal seizure are extremely variable, as may be gained from the accompanying records.

Sometimes (comparisons are made of lead 2 only) these complexes are aberrant and of the upright form, with unusually large T waves (fig. 2 *A*). Occasionally they are extremely bizarre, of low voltage and

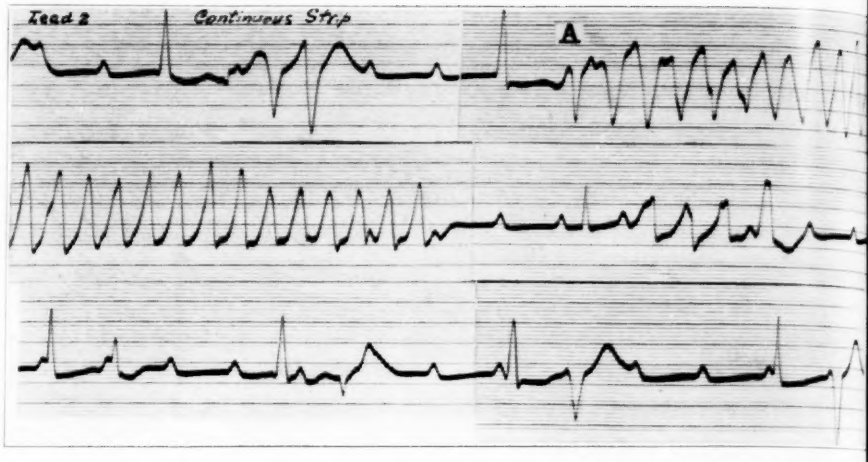

Fig. 4.—The premonitory period: The basic ventricular rhythm is interrupted by a series of aberrant ventricular oscillations (*A*), only the first four of which could be heard at the apex of the heart or felt at the radial pulse. During such periods of approximately eight seconds' duration, the patient's face was pale and her eyes were shut.

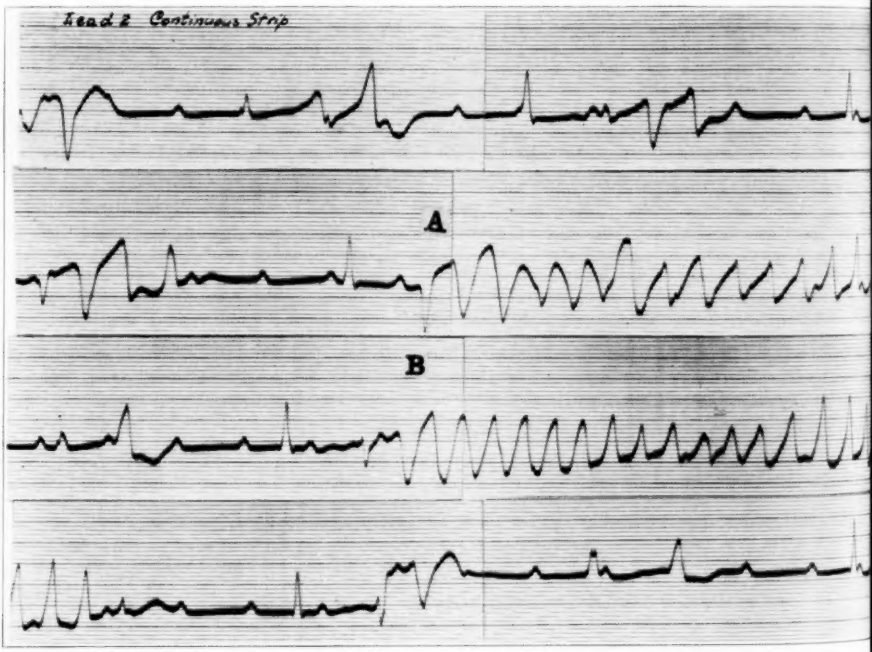

Fig. 5.—The premonitory period: Recurrent groups of aberrant ventricular oscillations of about five seconds' duration associated with a disappearance of the heart sounds and the pulse during their presence. Note that the ventricular deflection initiating these periods (*A*, *B*) is downward as a rule.

very wide (fig. 3 *A* and *B*). Most frequently, however, the initial deflection consists of an extrasystole that is practically always of the same shape and almost of the same size and form (fig. 2 *D*, fig. 3 *C*, fig. 4 *A* and fig. 5 *A*).

The electrical complexes that follow the initial ventricular beat are wide (0.32 second), aberrant deflections that resemble those seen in patients with disturbed conductivity in the bundle branches when the voltage is as high as 20 mm. (fig. 2 *E*, fig. 3 *C* and *D* and fig. 5 *A* and *B*) or approach closely records that resemble arborization block (fig. 6 *B*). Beat by beat they sometimes decrease in size as the frequency of the oscillations is increased, and at times they increase in size (fig. 3 *A* and *D*) for a few beats until they reach a standard size and sometimes remain so with but slight fluctuations throughout a seizure of syncope.

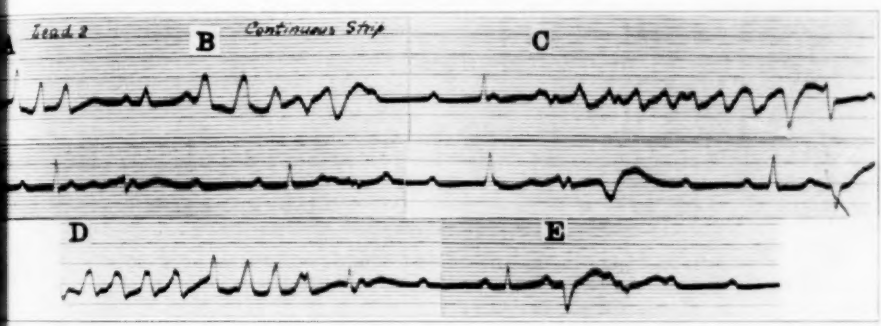

Fig. 6.—The premonitory period: When the voltage of the ventricular complexes of the basic rhythm is low, then the voltage of the aberrant ventricular oscillations appearing at such times is low. Compare 6*B*, *C* and *D* with 5*A* and *B* of the previous record.

The sequence of the auricular beats is not disturbed during these short runs in the premonitory period, although the auricular rate is occasionally increased and extra-auricular beats are produced, probably from the contraction of the extraventricular beats with retrograde conduction to the auricles.

THE CLINICAL MANIFESTATIONS DURING THE PRESENCE OF TRANSIENT VENTRICULAR FIBRILLATION

A major syncopal attack accompanied by convulsive movements of various parts of the body was usually preceded by several shorter periods of unconsciousness as described. If, after a strong beat at the pulse, pallor of the face was noted to follow a few progressively weaker beats with a disappearance of the pulse for at least twenty seconds, then a major attack could invariably be expected.

With this absence of the pulse, when no tremors could be palpated over the precordium and no heart sounds were audible, the respirations would begin to increase in frequency. At first both inspirations and expirations that averaged 40 per minute would be equal in duration. This period usually lasted for about one minute, during which time the patient was totally unconscious, and the face assumed a dark purplish discoloration.

The breathing was noted to become stertorous when the inspiratory phase was almost double the duration of expiration after about one minute following the onset of the attack. It was in this phase of breathing that all the noise (stertorous breathing) could be heard, for the mouth was shut tightly and the air could get in only through the nose, which, with the adjacent soft parts of the larynx, would be set into vibration.

After about one and one-half minutes, the muscles of the neck would stiffen, and short jerky movements of the head appeared at the same time that the hands, with both wrists bent over, would be raised involuntarily to the level of the head. Frequently short convulsive seizures would involve practically the whole body. These were accompanied at times by an opening of the eyelids, when the eyes could be seen to rotate in the same directions as the head.

After about two minutes all movements of the body would stop. The inspirations would become extremely labored, as seen usually shortly ante mortem, and the expiratory phase would be slightly increased. At the end of three minutes all breathing would stop. From forty to eighty seconds later, all muscles would relax, and the patient, intensely cyanotic, would appear practically dead.

It was common to observe such periods of unconsciousness last from four to six minutes. Spontaneous revival was usually associated with the appearance of a heart beat and suffusion of the entire skin over the body uniformly, immediately after its appearance. Respirations were not established until from 10 to 20 heart beats could be felt to come through at the wrists. At first the breathing would be shallow and slow, and then within a minute the normal phase would be reestablished progressively as the patient opened her eyes and frequently screamed out loudly, not realizing that she had passed through a phase of unconsciousness.

Her first comments on attaining full consciousness were incoherent and unintelligible, but within ten minutes after the onset of a seizure that would last as long as six minutes she became perfectly rational and always asked to be excused for soiling her linen.

Sometimes, she would immediately lapse into unconsciousness and go through exactly the phases described almost as soon as she was over the effects of one attack.

On several occasions, after the patient had lapsed into unconsciousness and her respirations had ceased for at least two minutes, we attempted artificial respiration. This could never be carried out until her muscles had relaxed completely. It was found possible at such times to push the fingers high up under the left costal margin and, by vigorous massage for about one minute, bring about effectual contractions of the ventricles, to be followed within from twenty to thirty seconds, as a rule, by normal respirations with gradual restoration of consciousness.[4]

THE ALTERATIONS IN THE ELECTROCARDIOGRAM DURING TRANSIENT VENTRICULAR FIBRILLATION

Repeated electrocardiograms taken during the syncopal seizures invariably revealed the cardiac mechanism to be due to ventricular fibrillation. A good idea of the type of ventricular oscillations encountered at such times may be gained from the accompanying electrocardiograms (figs. 7, 8, 9, 10 and 11). The electrical deflections were extremely variable from time to time. They were aberrant in form and were different in each attack, although they resembled each other closely during the same attack. (For example, compare the deflections in fig. 7 with each other and with those in fig. 9.)

The height of the electrical deflections varied from a minimal of 0.5 mm. (fig. 9 *A*) to 15 and 20 mm. (fig. 8 *Y*). Most of the records revealed a periodic waxing and waning in the height of the oscillations, but occasionally there were sudden and abrupt changes in the mechanism within the same record independent of these variations (fig. 9 *B*).

The height of the ventricular complexes during the presence of the basic rhythm preceding a period of ventricular fibrillation seemed to bear some relationship to the height of the oscillations during the presence of ventricular fibrillation. The same is true of the voltage of the complexes of the idioventricular beats following recovery from a period of ventricular fibrillation.

Infrequently some of the waves would seem to be alternately higher, so as to give the impression of electrical alternation (fig. 8 *A*, *B*, *C* and *D*).

The frequency of the oscillations varied from 150 to 500 per minute, depending on the height of the waves, for those of greater voltage (fig. 8) were also of longer duration individually than those of lower voltage (fig. 7 *B*).

Toward the end of each seizure the duration of all the oscillations increased, so that the frequency, as a rule, likewise decreased.

4. In the light of further experiences we are not certain that massage as carried out by us was responsible for the revival of the heart.

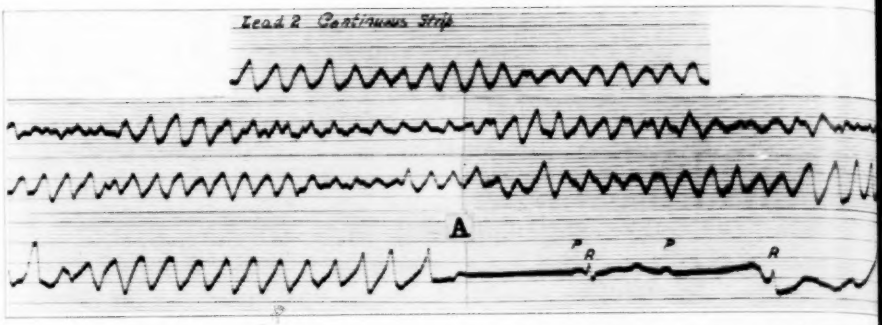

Fig. 7.—The fibrillatory period: A record obtained toward the end of a syncopal seizure lasting more than four minutes. The ventricular oscillations are aberrant; there is no definite base line between them; they vary in height, width, shape and form from beat to beat. Their frequency is between 200 and 500 per minute. There are a periodic waxing and waning of the oscillations throughout the record. This transient period of ventricular fibrillation ends with a postundulatory pause (*A*) and is followed by an intermediary idioventricular rhythm.

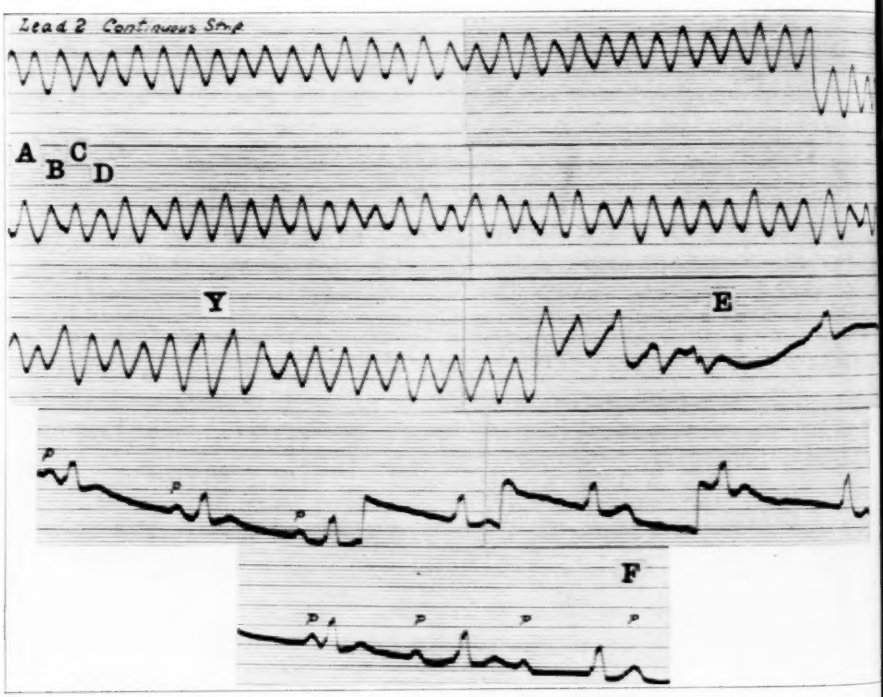

Fig. 8.—The fibrillatory period: A record obtained toward the end of a syncopal attack lasting about three minutes. The ventricular oscillations are wide, and at times there is evidence of electrical alternation (*A, B, C, D*). Their frequency is between 150 and 250 beats. Toward the end of the seizure, the complexes increase in height as well as in duration (*Y-E*). A postundulatory pause (*E*) is followed by an idioventricular rhythm, with a progressive increase in the ventricular rate from 48 to 130 beats per minute (see fig. 15) before there is restoration of the basic rhythm. Note that the auricular rate in the postfibrillatory period (*E-F*) is irregular. At times there is no evidence of any auricular contractions.

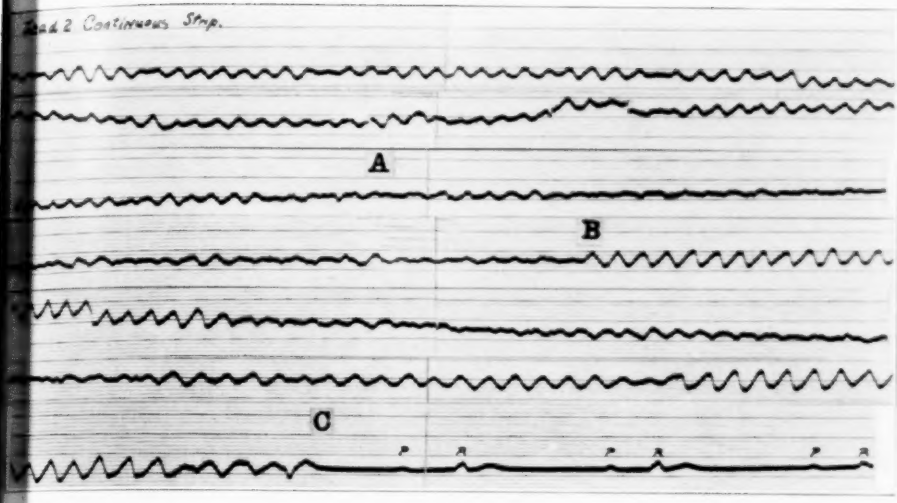

Fig. 9.—The fibrillatory period: A record obtained toward the end of a syncopal attack lasting more than five minutes. The ventricular oscillations are of low voltage, with a frequency varying from 200 to 400 per minute. Note the periodic waxing and waning in the height of the deflections. At *B* the oscillations are almost regular and resemble each other closely. The seizure ends with a postundulatory pause (*C*) and is followed by an intermediary idioventricular rhythm, with a progressive increase in rate from 25 to 93 beats per minute before there is restoration of the basic rhythm. The auricular rate in the postfibrillatory period keeps pace with the ventricular rate.

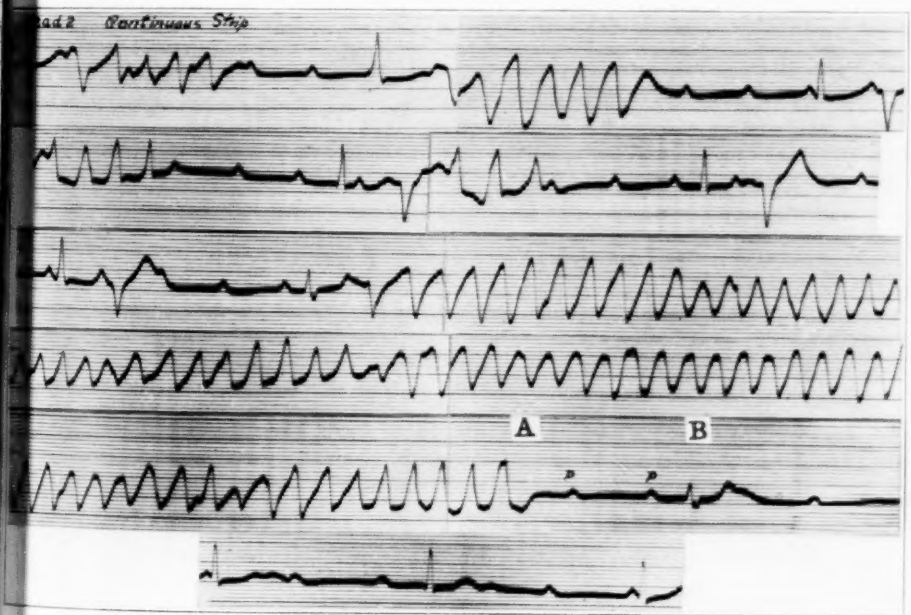

Fig. 10.—A continuous record, showing a premonitory period followed by a transient seizure of syncope lasting twenty-four seconds. The postundulatory pause (*A*) is followed by 2 auricular beats before the appearance of a single idioventricular beat. The basic rhythm follows immediately. The auricular sequence is apparently not disturbed during the presence of short runs of ventricular fibrillation.

During the longer syncopal seizures, the auricular contractions were not visible, and the mode of recovery from ventricular fibrillation seemed to bear no relationship to their presence, as was observed in the records of another patient.[1]

THE MODE OF RECOVERY FROM TRANSIENT VENTRICULAR FIBRILLATION

A period of transient ventricular fibrillation ceases promptly and is usually ended by a postundulatory pause, varying in duration from one-half to one and a half seconds (fig. 7 *A*, fig. 8 *E*, fig. 9 *C*, fig. 10 *A*, fig. 11 *B* and fig. 12 *B*). This pause may be followed by 1 (fig. 9 *C*), 2 (fig. 11 *B* and fig. 12 *B*) and sometimes 3 auricular beats before the

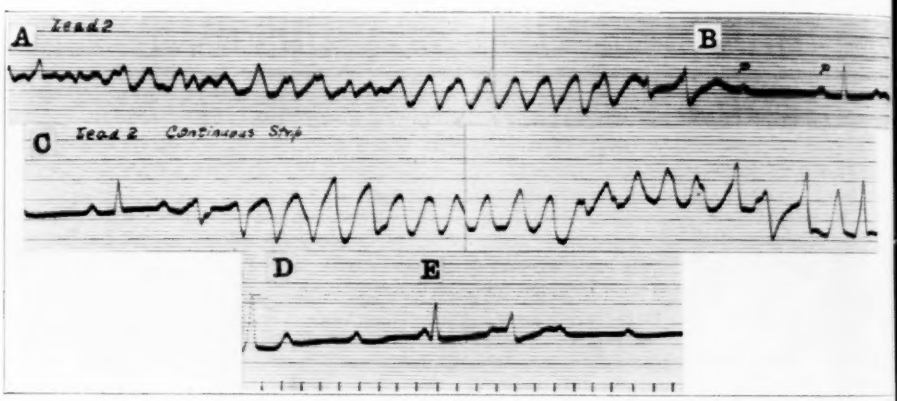

Fig. 11.—*A*, the end of a syncopal seizure, lasting a little over one minute. *B*, a short postundulatory pause is followed by 2 auricular beats and the basic rhythm is reestablished immediately. *C*, a short period of ventricular fibrillation followed by the basic rhythm (*D-E*) without the presence of a postundulatory pause.

ventricles begin to contract effectually again (11 *D*). Occasionally no auricular contractions may be seen at all preceding such a period of recovery (fig. 8 *E*).

The basic rhythm may appear immediately after these initial auricular beats (fig. 11 *B* and fig. 12 *B*). More often, however, especially if the syncopal seizure has been longer than one minute, an idioventricular rhythm with an irregular rate and complexes totally different from those of the basic rhythm precedes the development of the usual rhythm.

THE POSTFIBRILLATORY PERIOD

The end of a major syncopal attack due to transient ventricular fibrillation may be appreciated clinically by the appearance at the radial

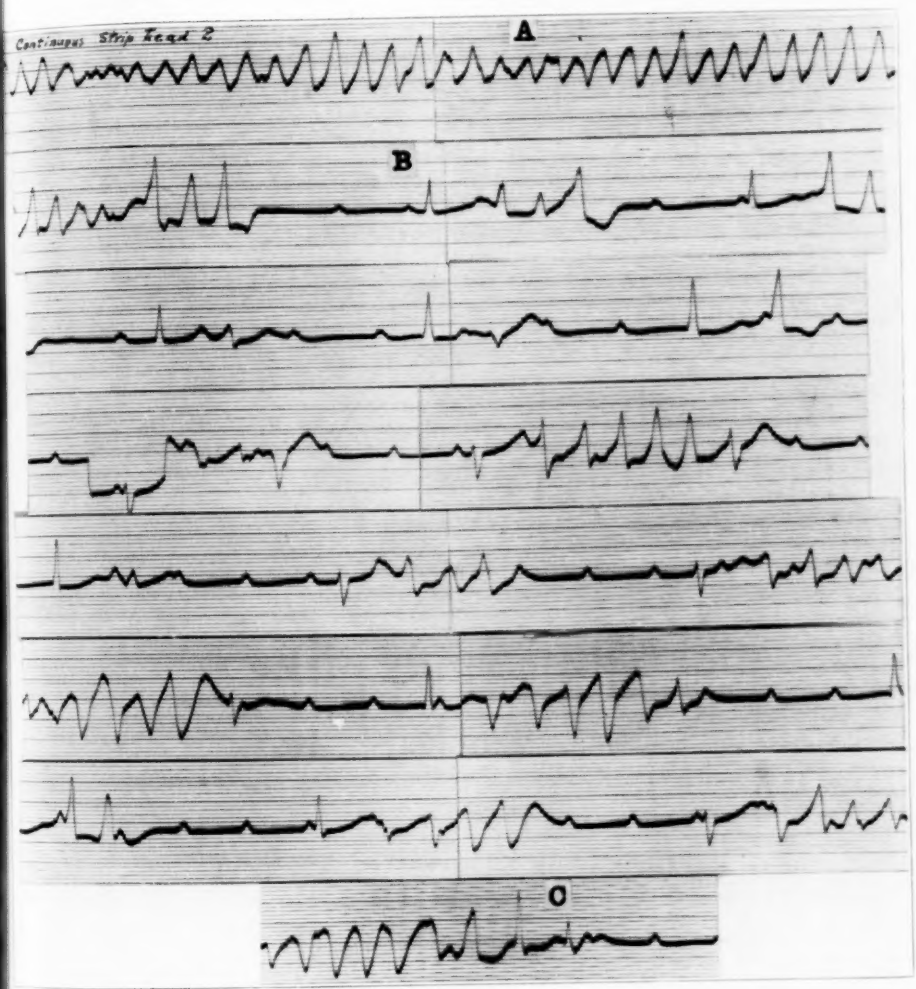

Fig. 12.—The postfibrillatory period: *A*, the end of a syncopal seizure may be followed at times by a series of recurrent groups of ventricular oscillations (*B-C*) resembling the premonitory period. (Compare this record with fig. 2). As a rule, such records herald the approach of another transient syncopal attack.

pulse of a beat that can barely be heard at the apex of the heart. The color of the skin changes immediately after this from a dusky cyanosis to a reddish hue. Beat by beat the sounds become audible at the apex, and the pulse becomes fuller.

The ventricular rate of the intermediary idioventricular rhythm during the period of recovery increases at times progressively from as low as 25 beats per minute at the end of a seizure of ventricular fibrillation to 93 beats, one and a half minutes later (in fig. 14 compare *A* to *B* and *C* to *D*) before there is a sudden transition to the usual rate of from 28 to 38 beats per minute (fig. 14 *E*). Often the rate of the ventricles during the postfibrillatory period is not as high, averaging

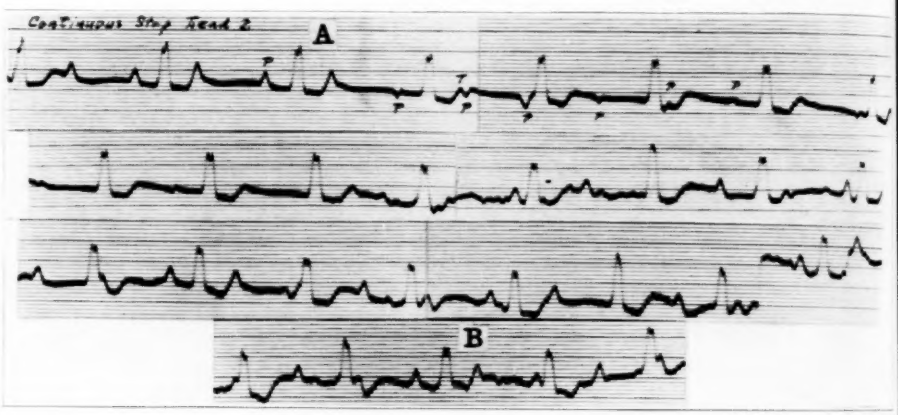

Fig. 13.—The intermediary idioventricular rhythm obtained fourteen seconds following a long syncopal seizure. The ventricular complexes are aberrant. The ventricular rate increases progressively from 37 to 95 beats per minute. The auricular rate is likewise irregular. At times the auricular complexes are variable in shape, size and form.

only 37 beats (fig. 13 *A*), or 48 beats (fig. 15 *A*) immediately following the postundulatory pause, and may not reach more than an average of from 50 to 55 beats (fig. 13 *B*) before the restoration of the basic rhythm.

Only rarely is a period of "tachysystole" observed during this time, when the ventricular rate may be as high as 136 beats per minute (fig. 15 *B*), each beat coming through at the radial pulse, however.

Again the postfibrillatory period may resemble in every respect the period preceding a transient seizure of ventricular fibrillation. (Compare fig. 12 *B* to *C* with fig. 2 *C* to *E*.)

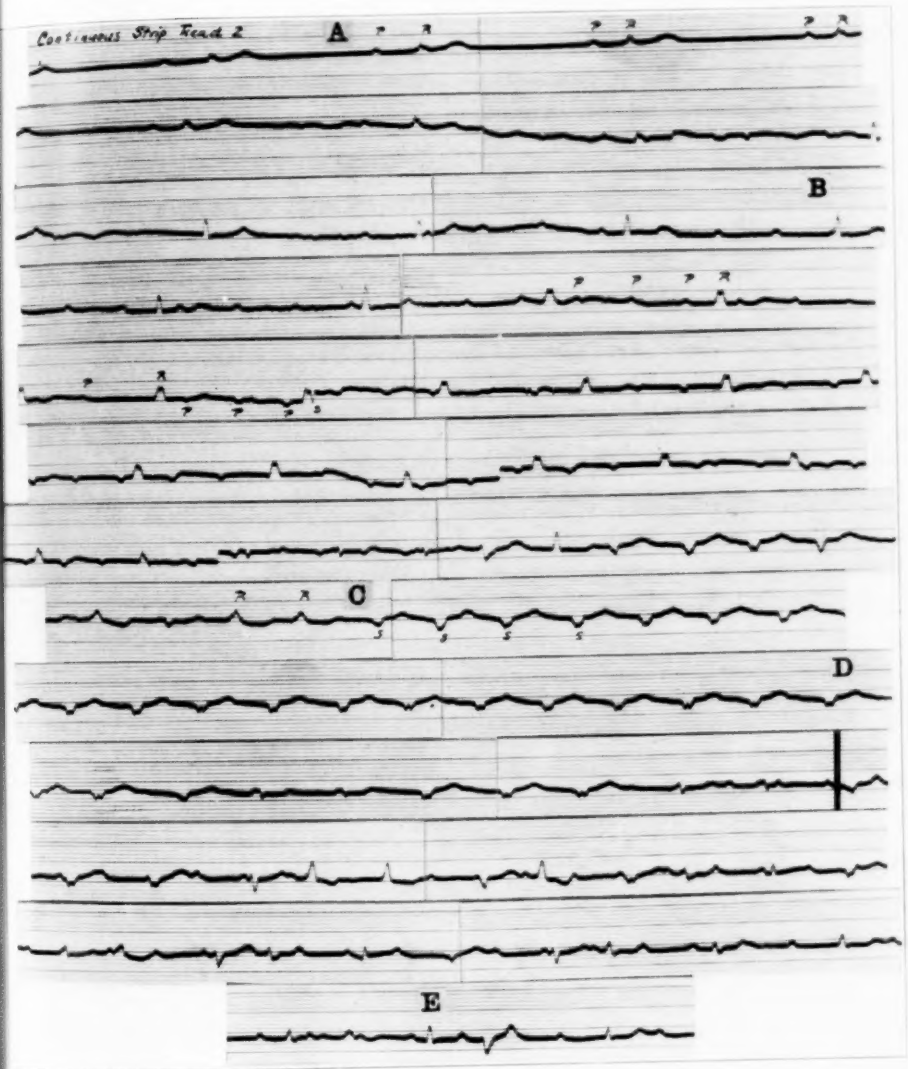

Fig. 14.—The intermediary idioventricular rhythm (this record is continuous with that of fig. 9). Note the progressive increase in the ventricular rate from 25 to 93 beats per minute. Compare the ventricular complexes with each other and with those of the previous record. There is a constant shifting of the idioventricular pacemaker until the restoration of the basic rhythm. The voltage of these ventricular complexes is low as compared with those of figure 13.

The postfibrillatory period usually lasts about one minute, when the normal respiratory sequence is established again and the patient regains full consciousness.

The voltage of the ventricular complexes forming the idioventricular rhythm is variable from record to record (fig. 13 *A*, fig. 14 *A* and fig. 15 *A*) and seems to bear some relationship to the size of the electrical deflections during the period of ventricular fibrillation preceding it. These complexes are aberrant in form and vary in the same record

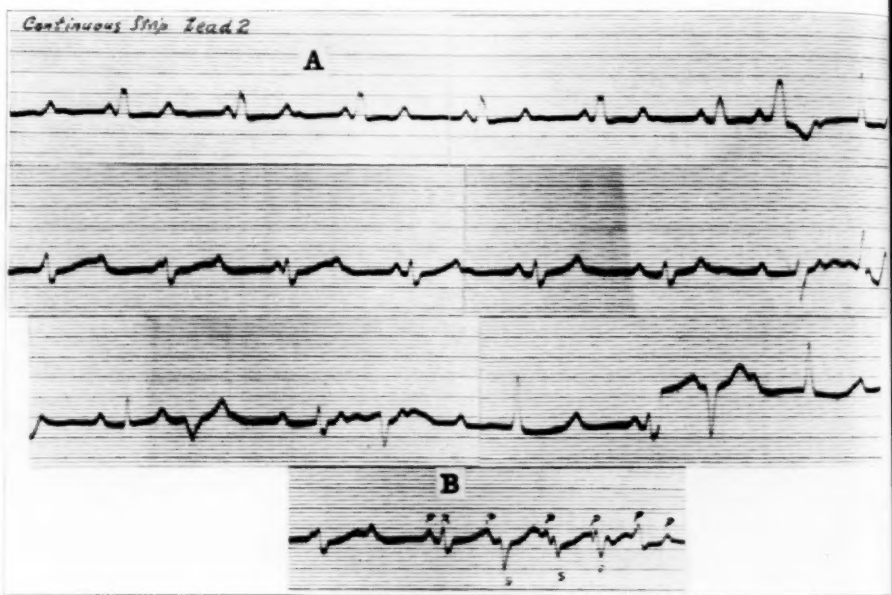

Fig. 15.—The intermediary idioventricular rhythm shows variable ventricular complexes. Infrequently a "tachysystole" follows one of these attacks when the ventricular rate rises to 136 beats per minute. The auricles keep pace with the ventricles.

(fig. 14 *A*, *B* and *C* and fig. 15 *A* and *B*), indicating a change in the pacemaker of the ventricles until the reestablishment of the basic rhythm.

During this period the auricles may keep pace with the ventricles (fig. 15 *B*), or the P waves may be totally absent (fig. 8 *E* and *F* and fig. 14 *C*). Often they too show a change in their pacemaker (fig. 13 *A*), but their presence or absence seems to bear no relationship to the return to normal of the basic ventricular rate.

SUMMARY

1. A clinical and electrocardiographic study was made of the syncopal seizures in a patient with auriculoventricular dissociation. More than a hundred electrocardiograms obtained during such seizures revealed the cardiac mechanism to be due to transient ventricular fibrillation.

2. The natural periods of transient ventricular fibrillation in this patient have varied in duration from only a few seconds to six minutes each, and as many as two hundred and seven attacks of unconsciousness have been observed during a period of twenty-four hours with spontaneous revival. During a period of four months' observation, not a single day passed without the patient experiencing at least one attack.

3. The premonitory periods preceding a transient seizure of ventricular fibrillation of the ventricles have been variable. They consisted at first of alternate premature beats of the ventricles, which increased the basic ventricular rate. These were followed shortly by irregular periods of recurring groups of aberrant ventricular oscillations, only the first few of which could be heard at the apical region of the heart or felt at the radial pulse.

4. Pallor of the face and momentary loss of consciousness followed the appearance of these recurrent groups of ventricular oscillations when, during their presence, the pulse disappeared for more than eight seconds but for not more than twelve.

5. A major attack of unconsciousness with cyanosis, stertorous breathing and convulsions took place when the heart sounds and pulse disappeared for at least twenty but not less than forty seconds. The electrocardiograms made during these periods invariably revealed ventricular fibrillation.

6. The frequency of the ventricular oscillations during the periods of transient ventricular fibrillation varied from 250 to 500 per minute.

7. Spontaneous revival from a seizure of ventricular fibrillation was usually ushered in by the appearance in the electrocardiograms of a postundulatory pause, which was followed by an intermediary idioventricular rhythm, as a rule, with an increasingly irregular rate before the restoration of the basic ventricular rhythm.

8. It is important to appreciate that syncopal seizures in patients with auriculoventricular dissociation are much more commonly associated with transient periods of ventricular fibrillation than has been suspected hitherto.

9. Rational therapy for the prevention of syncopal seizures in patients with auriculoventricular dissociation depends on an intimate knowledge of the cardiac mechanism underlying these seizures.

LOCALIZATION OF AFFERENT VISCERAL IMPULSES IN THE SPINAL CORD

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AND

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In 1922, one of us (S. W.) and Hatcher [1] located two small symmetrical areas on the floor of the fourth ventricle in cats, corresponding to the sensory nuclei of the vagus nerves. The application of unusually small amounts of certain drugs to these areas promptly induced nausea and vomiting, whereas local depression by drugs or mechanical injury abolished this response. This finding indicated that the sensory nuclei of the vagi are essential to the mechanism of vomiting, whether of central or peripheral origin. It was further shown that vomiting could be induced by peripheral stimulation of a viscus after vagotomy or by stimulation of an organ not supplied by the vagus nerve.[2] These observations indicated that both the vagus and the sympathetic fibers of the autonomic nervous system carry afferent impulses to the so-called vomiting center, and that vomiting can be induced reflexly through either path. The concept that the autonomic nervous system is subdivided into a sympathetic and a parasympathetic system seemed, therefore, to be as justifiable for the sensory part of the autonomic nervous system as Langley [3] has suggested it is for the motor portion. Hatcher and one of us (S. W.) [4] further demonstrated that vomiting is always a reflex that is induced (1) by the local action of physical or chemical

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) of the Boston City Hospital, and the Department of Medicine, Harvard Medical School.

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2. Weiss, S., and Hatcher, R. A.: The Mechanism of the Vomiting Induced by Antimony and Potassium Tartrate (Tartar Emetic), J. Exper. Med. **37**:97, 1923.

3. Langley, J. N.: The Autonomic Nervous System, Cambridge, England, W. Heffer & Sons, Ltd., 1921, part 1, pp. 1 and 28.

4. Hatcher, R. A., and Weiss, S.: Studies on Vomiting, J. Pharmacol. & Exper. Therap. **22**:139, 1932.

agents on the center, which is excited to such an extent that normal afferent impulses produce a reflex discharge of the motor impulses characteristic of vomiting (central vomiting), or (2) by the action of abnormal peripheral impulses on the center which is stimulated to discharge impulses that produce vomiting (peripheral vomiting).

These facts suggested that severance of the afferent path at any point would abolish vomiting and that the presence or absence of the vomiting response could be used as an index of the integrity of the afferent path. The present study was therefore undertaken with the hope that this method would localize the afferent path of the vomiting reflex in the spinal cord, and that this path would suggest, possibly, the site of other afferent visceral tracts and offer a new approach to the study of this aspect of the autonomic nervous system.

METHOD OF INVESTIGATION

Vomiting induced by digitalis bodies was selected as an experimental reflex suitable for use in determining the seat of afferent impulses in the cord, as this mechanism had been studied in detail by Hatcher and one of us (S. W.).[5] It was shown that large doses of digitalis bodies applied locally to the vomiting center in the medulla of cats did not produce vomiting as did other emetics, such as nicotine and apomorphine hydrochloride. In contrast, a single intravenous dose of digitalis produced prolonged nausea and vomiting. It was pointed out that vomiting produced by digitalis poisoning is a reflex the peripheral seat of action of which is in the heart or its adjacent structures. This concept was further substantiated by perfusion experiments in which the intact brain was essentially excluded from the heart and trunk. When the brain so prepared was perfused with defibrinated blood containing ouabain, vomiting did not occur, but when the same animals were given intravenous injections of ouabain, which was prevented from reaching the medulla, emesis resulted. Furthermore, it was demonstrated that vomiting caused by digitalis was abolished soon after complete denervation of the heart, and that the same abolition of vomiting occurred after large doses of nicotine.[6] Complete section of the cord at the level of the first thoracic vertebra in vagotomized cats also prevented vomiting. Section in this region of the cord would, of course, intercept fibers coming from the heart through the inferior cervical sympathetic ganglion and passing to the medulla through the cervical cord.

5. Hatcher, R. A., and Weiss, S.: The Seat of the Emetic Action of the Digitalis Bodies, Arch. Int. Med. **29**:690 (May) 1922; Reflex Vomiting from the Heart, J. A. M. A. **89**:429 (Aug. 6) 1927; The Seat of the Emetic Action of the Digitalis Bodies, J. Pharmacol. & Exper. Therap. **32**:37, 1927.

6. Hatcher and Weiss (footnote 5, third reference).

TECHNIC

All experiments were carried out on adult cats, which were anesthetized with ether. To intercept any impulses that might make their way to the cord through the stellate ganglions, the spinal cord was selectively injured in the region of the fifth and sixth cervical vertebrae. Double vagotomy was performed, and tracheal cannulas were inserted. The cervical vertebrae were then exposed. With the aid of bone rongeurs the spinous processes of the fifth or sixth cervical vertebra were removed. The cord was gently moved to the side and the lamina of the vertebra removed laterally to the transverse processes on both sides. This method of exposure was sufficient for injury to the dorsal and lateral columns of the spinal cord. To section the anterior column, it was necessary to cut off the anterior arches of the vertebrae and expose as much of the ventral surfaces of the cord on each side as possible. In the first experiments, involving injuries to the anterior column, one section was made on each side of the anterior fissure. This was rather unsatisfactory, for it was difficult to gage the extent of the damage, and it was important that the damage on both sides should be symmetrical. Furthermore, the removal of both anterior arches increased operative shock and hemorrhage which, when extensive, left the animals depressed. A depressed animal generally fails to vomit after any powerful emetic. This first technic was then modified to the exposure of the lamina, transverse processes and the arch of the vertebra on one side only, and a single anterior section was made with a specially shaped knife. Hemorrhage from veins about the spinal cord was controlled by very light pressure. The hemorrhage was slight in some experiments, and considerable in others. Massive local hemorrhage and subsequent depression excluded the use of an animal in these experiments. In each experiment the subdural and subarachnoid spaces were opened, and the spinal fluid was allowed to escape. After the injury was inflicted, the dura was approximated and the muscle layers and skin were carefully closed and sutured. The animals were then placed in a warm cage for recovery. When the operative procedure and duration of anesthesia were relatively short, i. e., less than one and a half hours, and attended with slight hemorrhage, the animals were generally in good experimental condition within three or four hours. Their condition was studied by noting spontaneous movements, alertness and reactions to visual and auditory impressions and pain stimuli. When such observations showed that the general condition of the animals was satisfactory, a fatal dose of one of the digitalis bodies was given intramuscularly, and the animal was kept under constant observation for signs of nausea or vomiting, which almost regularly precede death from digitalis in animals in good condition.[7] From 10 to 20 cc. of the tincture of digitalis or from 3 to 6 mg. of strophanthus was injected into the gluteal muscle. This dose was repeated, and the animal was watched until death from digitalis poisoning supervened. It was repeatedly observed that the intramuscular absorption of digitalis bodies was slower after injuries to the spinal cord. Following the death of the animals the cord in the region of the injury was carefully removed and lampblack applied to the site of the injury to make identification easier. The spinal cords were placed in 10 per cent formaldehyde and serial sections made. After the section had been stained, a composite diagram was made of the extent of the injury. Injuries consisting of narrow, stablike wounds, which involved the posterior column with

7. In an earlier group of experiments an effort was made to study vomiting induced by gastric irritants, such as corrosive mercuric chloride. However, the passing of the stomach tube with its attendant excitement after the extensive operative procedure was often sufficient to cause a subsequent inhibition of vomiting. This procedure was then abandoned, and digitalis in the form of a tincture or a solution of strophanthus was regularly used.

the tracts of Goll and Burdach, often did not gap, and it was therefore difficult to gage the extent of damage in such experiments. In some experiments, indeed, there was such complete reapproximation of the two injured surfaces that the injury could not be identified in the serial sections. Injuries to the lateral and ventral columns usually showed an unmistakable gap.

RESULTS

Sixty-four experiments were performed on adult cats. Complete transverse section of the cervical and upper thoracic spinal cord was first carried out in control experiments to be sure that the afferent sympathetic impulses did traverse the spinal cord, and that its section would prevent their transmission. The condition of six animals used for this test was good approximately four hours after the operative procedure. In five of the animals the section ran transversely between the fifth and sixth cervical vertebrae; in one, at the level of the second thoracic vertebra. Vomiting did not occur after the administration of fatal doses of digitalis to these animals. It seems probable that the absence of vomiting was not due to depression.

Complete sections of the posterior column were performed in ten animals, and were satisfactory for analysis. In seven there was definite vomiting or retching before the typical digitalis death. In one, there was unmistakable evidence of nausea approximately one minute before the final convulsion. The animal licked his lips rapidly, a characteristic sign of the nausea associated with vomiting.[4] No evidence of nausea or vomiting appeared in two of the ten animals. In one the injury was found to involve more than the posterior column, with evidence of pyramidal paralysis as well as posterior column ataxia. There was no explanation for the other animal's failure to vomit. The animal was apparently in good condition, and died a typical digitalis death. In operating on this animal great care had been taken to confine the incision to the posterior column, but it is possible that the tip of the blade penetrated more anteriorly than could be determined from the serial section. All ten animals showed the usual responses to pain stimuli. The results of these experiments showed that the posterior column does not contain the path that carries the afferent impulses responsible for digitalis vomiting. The protocols of two typical experiments follow:

EXPERIMENT 33.—Dec. 10, 1926. Male cat; weight 2.6 Kg.

2:50 p. m.: Ether anesthesia started.

3:20 p. m.: Spinous processes and lamina up to the lateral vertebrae removed, and section of the posterior columns of Goll and Burdach completed.

3:30 p. m.: Muscle layers and skin sewed.

3:45 p. m.: Double vagotomy, with insertion of tracheal cannulas, performed.

4:15 p. m.: Animal out of anesthesia.

8:15 p. m.: Animal in excellent condition. Responded to call promptly. Ran across floor with weakness of the hind legs and with ataxia. Attempted to escape from room. Pain responses present.

8:21 p. m.: 1.0 mg. of strophanthin per kilogram given intramuscularly.

8:58 p. m.: Rapid breathing started.

9:01 p. m.: Animal moved about.

9:02 p. m.: Respiration suddenly slowed down, and typical retching movements of vomiting developed.

9:13 p. m.: Animal died.

Cord removed and sectioned serially. Result of composite injuries of the section indicated that section involved the posterior column of Goll and Burdach and adjacent pyramidal tracts. One of the sections is reproduced in figure 1.

EXPERIMENT 36.—Jan. 15, 1927. Male cat; weight, 2.7 Kg.

2:45 p. m.: Ether anesthesia started.

3:00 p. m.: Spinous processes and laminae of the sixth and seventh cervical vertebrae removed and cord exposed.

3:25 p. m.: Rather extensive posterior section of the Goll and Burdach column, probably involving adjacent structures.

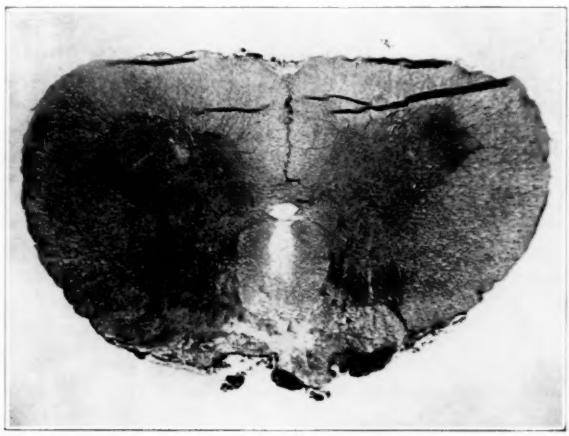

Fig. 1.—Injury of the posterior column of the spinal cord in experiment 33. This and more extensive injuries did not prevent vomiting.

3:30 p. m.: Tracheotomy performed; cannula inserted; double vagotomy performed.

6:00 p. m.: Animal answered call quickly; lifted head, but was unable to stand on four legs.

6:10 to 7:10 p. m.: Twenty milligrams of ouabain given in divided doses. Immediately after each injection, the animal struggled with considerable excitement, indicating pain reaction.

6:50 p. m.: Retching movements of the thorax and abdomen.

6:55 p. m.: Retching movements again.

7:15 p. m.: Typical digitalis convulsions and death.

Cord removed. Lampblack dusted into the sectioned area. Composite study of serial section indicated that injury involved almost the entire posterior half of the cord, extending anteriorly over the central canal. A section typical of this group is shown in figure 2.

Both lateral columns of the spinal cord were sectioned in five animals. In all five there was typical digitalis vomiting. In two additional instances the condition of the animals was considered only fair. After the injection of digitalis, these two animals showed an unusual degree of excitement and respiratory stimulation. Vomiting did not occur in either. It is possible that the excitement, with its attendant respiratory stimulation, was the cause of the inhibition. It has been shown by Openchowski [8] that rapid respiration inhibits vomiting. Previous observations [4] indicated that rapid respiration, pain and scratch reflexes are also capable of inhibiting the vomiting reflex. In this group of experiments, in spite of extensive injury which involved the lateral cerebellar and pyramidal tracts, vomiting was not prevented. It was clear, therefore, that injury to a large part of the cord in itself was not sufficient to inhibit vomiting.

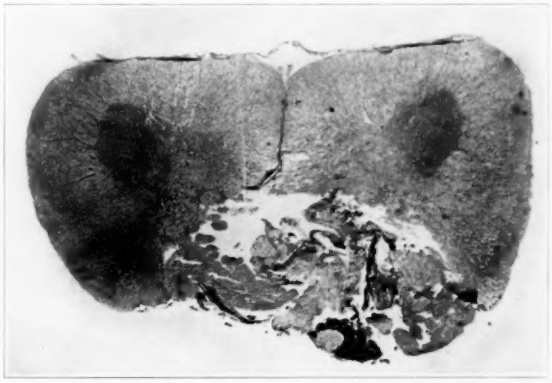

Fig. 2.—Injury of the posterior column of the spinal cord in experiment 35. This type of injury did not prevent vomiting.

These experiments indicated that the path of vomiting was not in the lateral columns. A protocol of a typical experiment follows.

EXPERIMENT 30.—Nov. 14, 1926. Male cat; weight 3 Kg.

2:12 p. m.: Administration of ether started.

2:20 to 2:40 p. m.: Posterior lamina of the seventh cervical vertebra removed. Practically no bleeding.

3:01 p. m.: Lateral sections in the region of the seventh cervical vertebra made. Small amount of spinal fluid escaped.

8:20 p. m.: Animal in fairly good condition. Crawled on his stomach with a certain amount of ataxia. Attempted to climb into a chair.

8:23 p. m.: Tincture of digitalis, 3 cc., injected.

8.35 p. m.: Animal in good condition; crawled about. At times attempted to run across the room.

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8. Openchowski, T.: Ueber die nervösen Vorrichtungen des Magens, Zentralbl. f. Physiol. **3**:1, 1889.

9:04 p. m.: Tincture of digitalis, 2.4 cc., injected intramuscularly.
9:18 p. m.: Definite signs of nausea; animal vomited.
9:20 p. m.: Typical retching movements. Licked lips repeatedly.
9:22 p. m.: Retching and vomiting again.
9:24 p. m.: Convulsions and typical digitalis death.

Following death, cord was carefully removed and serial sections were prepared. Composite diagram indicated that lateral columns up to gray matter were injured on both sides. Level of injuries was not exactly the same on both sides; hence in figure 3, which shows one of the sections of cord, only the one-sided injury is visible.

The anterior columns were sectioned in thirteen animals. The injury in these experiments involved mainly the sensory pathways running outside the anterior pyramidal tract in the anterior and lateral aspect of the

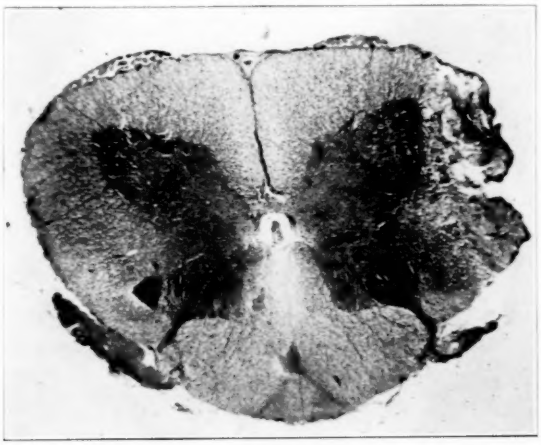

Fig. 3.—Injury of the lateral column of the spinal cord in experiment 30. This section shows part of the injury to the right lateral column. The similar injury to the left lateral column was not inflicted at exactly the same level and hence is not visible. This type of injury did not inhibit vomiting.

anterior column. The fibers of these areas have been shown to carry pressure, temperature and pain sensations.[9] In nine of these experiments vomiting failed to occur, although the animals were in excellent condition. In four instances there was unmistakable vomiting. Two lateral incisions had been made in these cases with the earlier technic, and the serial sections showed these to be incomplete as far as destruction of the entire anterior columns was concerned. The explanation for the presence of vomiting in these experiments was therefore obvious. In

9. Petrén, K.: Ueber die Bahnen der Sensibilität im Rueckenmark besonders nach den Fällen von Stickverletzung studiert, Arch. f. Psychiat. **47**:495, 1911. Rothman, M.: Zur Frage der Sensibilitätsleistung im Rueckenmark, Deutsche Ztschr. f. Nervenh. **43**:433, 1912.

seven of the nine experiments in which vomiting was abolished, it was found that the anterior and anterior lateral portions of the anterior column had been completely severed with one stroke. The response to pain in these animals was abolished. Protocols of two typical experiments with sections of the anterior columns of the cord follow.

EXPERIMENT 53.—June 9, 1927. Female cat; weight, 3.4 Kg.

6:05 p. m.: Ether started.

6:25 p. m.: Usual median line incision posteriorly. Muscle separated from both sides of the vertebral bony canal. Sixth and seventh spinous processes removed. On the left side the lateral bony wall to the median anterior line removed, thus exposing one half of the spinal cord. Anterior portion of the cord sectioned.

6:50 p. m.: Tracheotomy and double vagotomy performed.

9:45 p. m.: Animal in good general condition. Lifted self up and moved to opposite end of cage with ataxia.

10:10 p. m.: Strophanthin, 15 mg., injected intramuscularly.

10:20 p. m.: All pain responses abolished. Rather restless.

10:35 p. m.: Urinary incontinence and excitement.

10:36 p. m.: Death.

Cord removed and serially sectioned. Histologic examination indicated that injury involved anterior and anterior lateral columns. One of the sections is reproduced in figure 4.

EXPERIMENT 59.—March 24, 1928. Cat; weight, 2.58 Kg.

6:35 p. m.: Ether anesthesia started. Cord exposed as in experiment 53. Section of anterior column of the cord. Vagotomy and tracheotomy.

7:30 p. m.: Operation completed.

9:00 p. m.: Animal in good condition. Moved all four extremities, but was unable to walk because of marked ataxia; crawled about. Strophanthin, 3 mg., injected intramuscularly.

9:24 p. m.: Animal had typical digitalis convulsion and died without any evidence of nausea or vomiting. Serial section indicated that injuries involved anterior and lateral columns. One section of the cord with injury is reproduced in figure 5.

The failure of severance of both the posterior and the lateral columns to abolish the vomiting produced by digitalis points to the anterior column as the pathway of afferent impulses. The abolition of vomiting by section of the anterior column further confirms the localization in this region of the spinal cord.

COMMENT

The autonomic nervous system hitherto has been regarded largely as an efferent system. Langley,[3] in defining the autonomic nervous system, said: "The autonomic nervous system consists of nerve cells and nerve fibers, by means of which efferent impulses pass to the tissues other than multi-nuclear striated muscle." Later he also stated: "The facts show that there is a close relation between the action of the drug and the innervation of sympathetic and parasympathetic nerves respectively, and they suggest that there is a fundamental difference between the two systems."

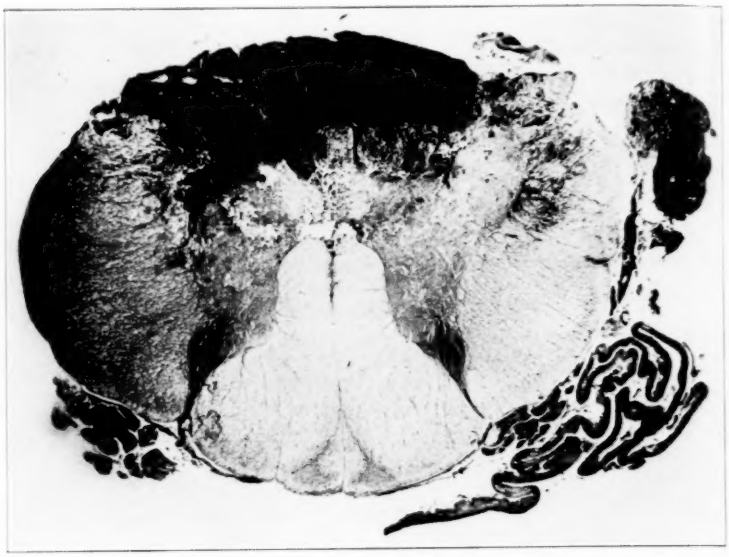

Fig. 4.—Injury of the anterior column of the spinal cord in experiment 53. This and less extensive injuries inhibited vomiting.

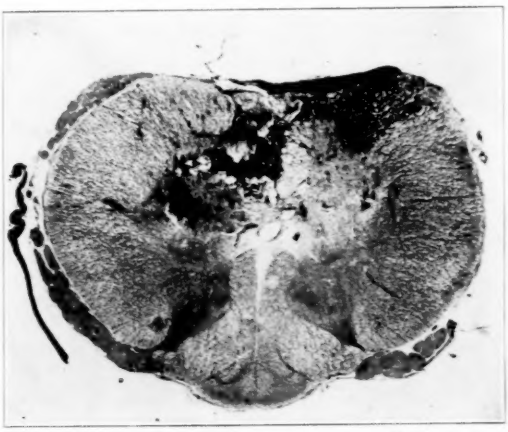

Fig. 5.—Injury of the anterior column of the spinal cord in experiment 59. This injury inhibited vomiting.

Hatcher and one of us (S. W.), in 1923,[4] summarizing experiences with the afferent visceral impulses involved in vomiting, stated: "The results of our experiments indicate that the efferent fibers concerned with emesis may be classified as sympathetic and parasympathetic with as much reason as the efferent, for atropine, pilocarpin and ergotoxin induce impulses which traverse these just as selectively as they act on the efferent end apparatus." The results of the present study indicate that both sympathetic and parasympathetic visceral afferent impulses induced by digitalis bodies, and perhaps by other emetics, enter the cord through the sympathetic chain and run up to the higher sympathetic centers in the anterior column.

In 1926, Spiegel[10] reported that the inhibition of respiration produced through dropping a concentrated barium chloride solution on the stomach and small and large intestine or through electric stimulation of the splanchnic nerve cannot be prevented by bilateral section of the posterior columns of Goll and Burdach or of the cerebellar tracts. This respiratory inhibition is abolished, however, by sectioning the anterior column or the anterior aspects of the lateral columns. His experiments are therefore in harmony with our observation that the visceral efferent impulses run in the anterior and lateral portion of the anterior column. Whether these afferent impulses are carried within narrowly definable tracts or traverse a relatively wide area cannot be stated. It is of interest, however, that the same area of the cord carries the visceral afferent impulse to the vomiting and respiratory centers and the somatic afferent sensations of touch, pain and temperature. Our previous observations[11] show that afferent cutaneous impulses have a close relationship to the mechanism of visceral pain, and that visceral pain induced by abnormal afferent sympathetic impulses may cease completely if the corresponding afferent impulses from the skin are blocked. These facts suggest that the close relationship between the autonomic and somatic afferent impulses in the spinal cord is not only structural but also functional.

SUMMARY AND CONCLUSIONS

1. The pathway of the afferent impulses of the vomiting reflex is located in the centripetal tracts of the anterior column of the spinal cord.

2. A close structural and functional relationship between afferent visceral and certain afferent somatic impulses in the spinal cord is suggested.

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10. Spiegel, E. A.: Experimentelle Grundlagen zur Chordotomie, Deutsche Ztschr. f. Nervenh. **89**:18, 1926.

11. Weiss, S., and Davis, D.: The Significance of the Afferent Impulses from the Skin in the Mechanism of Visceral Pain, Am. J. M. Sc. **174**:517, 1928.

DIURETIC EFFECTS AND CHANGES IN BLOOD AND URINARY METABOLITES AFTER DIGITALIS IN NORMAL AND IN EDEMATOUS PERSONS

A. B. STOCKTON, M.D.
SAN FRANCISCO

In recent experimental and clinical studies of diuretics, much attention has been devoted to correlation of quantitative changes in blood and urinary metabolites, especially the chlorides, with the object of determining the seat of diuretic action. The significance of the correlations has been about as follows: simultaneous increases in blood and urinary chlorides and in the output of urine reflect a direct and general action of the diuretic on the tissues, whereas a reciprocal change in the blood and urinary chlorides, i. e., a decrease in blood chlorides with a simultaneous increase in urinary chlorides and an increase in the output of the urine, reflect indirect effects through circulatory or renal changes, or both. These effects have been described for a number of diuretics, chemically and pharmacologically different. For instance, Hartzieganu, Gavrila and Borbil [1] demonstrated concurrent increases in blood and urinary chlorides during diuresis after mersalyl and merbaphen, in healthy and edematous human subjects. The same phenomena have been observed in healthy dogs and rabbits by Lyons,[2] using merbaphen, and by Curtis,[3] using theophylline. Lie [4] reported increases in the urinary chlorides during diuresis in a normal human subject receiving caffeine, but Lie did not investigate the blood chlorides. I have previously reported that bismuth sodium tartrate, merbaphen, mersalyl and theophylline, administered to human subjects,[5] and bismuth

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1. Hartzieganu, I.; Gavrila, I., and Borbil: Compt. rend. Soc. de biol. **99**: 1813, 1928.

2. Lyons, R.: M. Clin. North America **12**:1341, 1929.

3. Curtis, G. M.: Action of Specific Diuretics, J. A. M. A. **93**:2016 (Dec. 28) 1929.

4. Lie, E.: Am. J. Physiol. **92**:619, 1930.

5. Hanzlik, P. J.; Bloomfield, A. L.; Stockton, A. B., and Wood, D. A.: J. A. M. A. **92**:1413, 1929. Stockton, A. B.: Proc. Soc. Exper. Biol. & Med. **27**: 721, 1930.

given to rabbits,[6] caused simultaneous increases in the chlorides of the blood and urine during diuresis; the chlorides were generally unchanged in the absence of diuresis. The increase in urinary chloride was often not only an increase in the absolute daily amount, but actually an increase in concentration. Hence, it appeared that these diuretics acted directly on the body tissues, mobilizing chloride and water.

About the only other useful diuretic that has not been investigated in the light of the newer theories of diuretic action is digitalis. Cushny [7] suggested the desirability of studies on the effects of digitalis on metabolites. Recently, an attempt in this direction appears to have been made by Kellum and Keith,[8] but the results obtained on metabolites are not given in the abstract; they report only a variability in diuretic response and suggest the advisability of using other diuretics with digitalis in order to obtain satisfactory diuresis. In another abstract, Keith [9] stated that he has compared the changes in p_H, volume, chloride, total fixed base and nitrogen in urines of twelve normal men who received the following diuretics: digitalis, sodium nitrate, urea, sucrose, organic mercury compounds and theophylline-ethylenediamine and the chloride, nitrate and acetate of ammonium. It is stated that the diuretic effects were most marked after organic mercury and the chloride and nitrate of ammonium, and minimal after digitalis and ammonium acetate; the changes in metabolites are not mentioned. Experimentally, Hirsch [10] demonstrated increases in urinary chlorides, but no changes in blood chlorides in rabbits receiving various digitaloids, especially scillaren. Gremels [11] studied the actions of digitalis and various digitaloids on the heart-lung-kidney preparation; these drugs caused an increased excretion of water and chloride in the urine, but no increase of total nitrogen. Unfortunately, changes in the blood chlorides were not observed.

These various results on animals and on an excised system of organs suggest that digitalis, as a diuretic, acts differently than do the purines and metals. The conditions in normal animals, and in an excised organ system largely free of tissues, are not comparable with the conditions in which digitalis is used as a diuretic, namely, in edema of cardiac origin. While it is logical to expect that the diuretic action of digitalis would manifest itself for the most part through circulatory improvement, yet unexpected variations in the drug's action are a matter of common knowledge and a tissue action could not be finally excluded

6. Stockton, A. B.: Arch. internat. de pharmacodyn. et de thérapie **51**:52, 1931.

7. Cushny, A. R.: The Action and Uses in Medicine of Digitalis and Its Allies, New York, Longmans, Green & Company, 1925.

8. Kellum, E. L., and Keith, N. M.: J. Clin. Investigation **10**:667, 1931.

9. Keith, N. M.: J. Pharmacol. & Exper. Therap. **42**:260, 1931.

10. Hirsch, H.: Arch. f. exper. Path. u. Pharmakol. **160**:220, 1931.

11. Gremels, H.: Arch. f. exper. Path. u. Pharmakol. **157**:92, 1930.

until the question was tested. Therefore, it appeared desirable to make a study of the quantitative changes in metabolites of the blood and urine after digitalis in normal and edematous human subjects along similar lines as in previous studies of bismuth.[5] In addition to the chlorides, the changes in uric acid and sugar of the blood and urine were observed. It was thought that the changes in endogenous uric acid would reflect more direct and intimate actions of the drug on the tissues, as the result of effects on cellular or nuclear metabolism. Less was expected from the changes in dextrose on account of the uncontrolled carbohydrate intake and liver glycogen, although the observations were made for any results that might serve as supplementary evidence. Briefly, the clinical results obtained sustain the results of Hirsch and of Gremels on animals, and indicate that the mechanism of digitalis-diuresis is different from that of the purines and the metals.

METHODS

In all, twelve patients were used in this study. They were divided into four groups representing different conditions.

Normal.—Patients 3, 4 and 7 were normal so far as the circulatory system was concerned. Patients 3 and 7 suffered from dyspepsia of functional character. Patient 4 had no complaints, but voluntarily subjected himself to the observations.

Decompensation without Edema.—Patients 1, 2, 5 and 6 showed moderate degrees of cardiac decompensation, due, in patients 1, 2 and 5, to arteriosclerotic heart disease, and, in patient 6, to a rheumatic lesion of the mitral valve. These four patients showed no frank pitting edema, but had definite signs of chronic passive congestion.

Decompensation with Edema.—Patients 8, 10, 11 and 12 were markedly decompensated with definite pitting edema of the extremities and lower part of the back, and ascites. Auricular fibrillation, established by clinical signs and electrocardiographic examination, existed in patients 8, 10 and 12. Patients 8, 10 and 11 suffered from arteriosclerotic heart disease, and patient 12 from mitral stenosis of rheumatic origin.

Cirrhosis with Edema.—One patient (no. 9) had portal cirrhosis with ascites and pitting edema of the legs and back.

The patients of all groups were placed at absolute rest in bed for the duration of the observations. They were given salt-free and purine-free diets, and a constant daily fluid intake of 1,200 cc. Daily twenty-four hour specimens of urine were collected, and daily specimens of blood, secured before breakfast. The specimens were analyzed promptly after collection.

The control periods extended for varying periods of time, averaging six days before the administration of digitalis, with a range of from two to ten days. A short control period occurred only in patient 8, who was badly decompensated, and required the earlier use of digitalis. The control periods of the other patients were extended until the output of urine and the metabolites in the blood and urine remained at constant levels for three days.

The digitalis was given in the form of standardized powdered leaf in weighed capsules. The dose varied with the individual; administration was continued until signs of minor toxicity (usually loss of appetite and nausea, or vomiting) occurred. The doses ranged between 0.7 and 2 Gm., with an average of 1.2 Gm. for the group who showed no diuresis, and 1.4 Gm. for the group who showed diuresis. As has been frequently observed, the susceptibility of the patient to the same standardized digitalis leaf showed considerable individual variation. The edematous patients with cardiac disorders were able to take more of the digitalis without minor toxic symptoms than were the normal subjects, who proved to be the most susceptible group.

The chlorides of the blood were estimated by the method of Austin and Van Slyke,[12] those of the urine by the Seelman-Volhard method,[13] the blood sugar by the method of Somogyi[14] and the uric acid of the blood and urine by the method of Morris and Macleod.[15]

RESULTS

The per cent of changes for individual patients are presented in chart 1. The cross hatched blocks represent the maximum daily per cent of changes, i. e., the greatest daily variations found as compared with the controls. The solid blocks represent the average changes observed during the six days following the administration of digitalis as compared with the six-day controls preceding the digitalis; these data are referred to as the total per cent of changes. In considering the changes in the output of urine, and in the various metabolites, the total per cent of changes are more significant than the maximum per cent; the latter indicate the greatest changes that were obtained. The maximum per cent of changes are presented for general interest, and since they were in the same general direction as the average changes, the discussion will be largely according to the average or total changes which are more conservative.

12. Austin, J. H., and Van Slyke, D. D.: J. Biol. Chem. **41**:345, 1920.

13. Seelman, J. J.: J. Lab. & Clin. Med. **1**:444, 1916.

14. Somogyi, M.: J. Biol. Chem. **83**:157, 1929; Proc. Soc. Exper. Biol. & Med. **26**:353, 1929.

15. Morris, J. L., and Macleod, A. G.: J. Biol. Chem. **50**:55, 1922.

As it was quite clear that definite groups of the patients showed diuretic action and others did not, chart 2 was prepared to illustrate correlations between the changes in the output of urine and in metabolites according to diuretic action or its absence in all twelve patients, regardless of condition. The solid blocks represent average changes in those patients showing increased diuresis, and the crossed block, average changes in those who did not. These correlations will be alluded to in

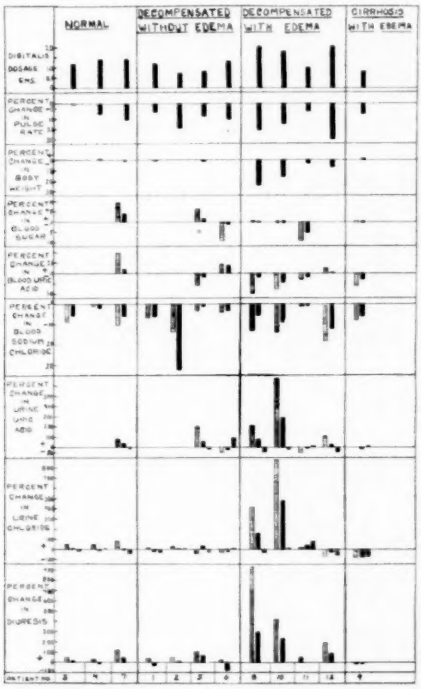
NORMAL
DECOMPENSATED WITHOUT EDEMA
DECOMPENSATED WITH EDEMA
CIRRHOSIS WITH EDEMA
DIGITALIS DOSAGE GMS.
PERCENT CHANGE IN PULSE RATE
PERCENT CHANGE IN BODY WEIGHT
PERCENT CHANGE IN BLOOD SUGAR
PERCENT CHANGE IN BLOOD URIC ACID
PERCENT CHANGE IN BLOOD SODIUM CHLORIDE
PERCENT CHANGE IN URINE URIC ACID
PERCENT CHANGE IN URINE CHLORIDS
PERCENT CHANGE IN DIURESIS
PATIENTS

Chart 1.—Per cent of changes in diuresis, blood and urinary metabolites, body weight and pulse rate after digitalis in normal and edematous subjects. The solid blocks in the figure, except as to dosage of digitalis, represent average total per cent of changes; the crossed hatched blocks, maximum daily per cent of changes, and the small squared blocks, average per cent of changes in concentration. The solid blocks in the sector on dosage represent total dosage of digitalis.

the text along with the average changes. Unless otherwise indicated, the per cent of changes discussed in the text refer to those of chart 1.

Diuresis.—The diuresis was variable in both normal and edematous subjects. It usually began on the second day after the digitalis was given (range from one to three days) and persisted during an average

of four days. In patient 8, the diuresis persisted for seven days. In the group of normal subjects, only one (patient 7) showed a diuretic action, namely, a total increase of 52.8 per cent. Patient 3 exhibited a total increase of only 3.8 per cent, and patient 4 showed a total decrease of 4.1 per cent in the output of urine.

Of the four decompensated patients without edema, two (nos. 2 and 5) showed slight increases, and two (nos. 1 and 6) showed decreases in total output of urine. The changes in total diuresis ranged between +70.6 per cent and —157 per cent, with an average of —26.9 per cent.

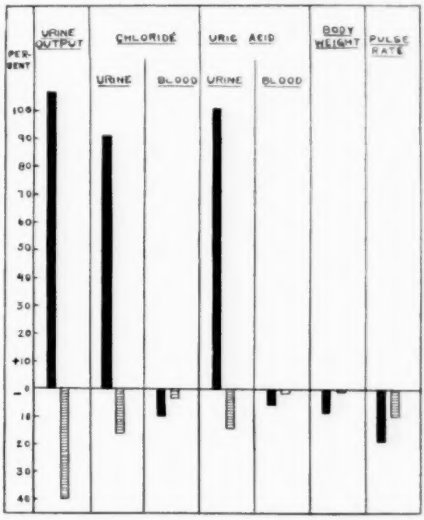

Chart 2.—Correlation of per cent of changes in urine output, blood and urinary metabolites, body weight and pulse rate according to presence or absence of diuretic action after digitalis. The solid blocks represent average total per cent of changes in patients showing marked diuresis and the crossed blocks, average changes in those in whom marked diuresis was not present.

As might be expected, the most active diuresis occurred in the group of edematous patients with cardiac disorders. The total diuresis ranged between 0 and 293.3 per cent, with an average of 154.9 per cent. In patient 8, the urine showed a maximum increase on one day of 923.3 per cent; actually, the diuresis removed over 11.5 liters of fluid during the seven day period. One of the definitely decompensated patients (no. 4) showed no change whatever in total diuresis, although his cardiovascular function was markedly improved by digitalis medication.

Patient 9, with portal cirrhosis and edema, showed a diminution in total output of urine, namely, — 13.2 per cent. During the period of observation his edema definitely increased.

Body Weight.—From chart 1 it is obvious that only the group of decompensated patients with edema showed a marked loss of body weight. This loss was greatest for patient 8, who also showed the most active diuresis: this patient lost 23.7 per cent of his body weight, or 34.5 Kg. (75.9 pounds) in seven days. Chart 2 illustrates the differences in loss of body weight of subjects with and without diuresis; the former showed a much greater loss of weight.

Chlorides.—The twenty-four hour output of chlorides in the urine varied directly as the diuresis. The greatest total increases were observed in patients 8 and 10, namely, 156.2 and 473.9 per cent, respectively. Only patient 12 showed diuresis with a decrease of urinary chloride. When diuresis failed to occur, or when the urine decreased in amount, the urinary chlorides were invariably decreased (chart 2). With the increase in twenty-four hour excretion of chlorides, there was sometimes an increase in the concentration of chloride in the urine (patients 10 and 11).

The blood chlorides showed a decrease in all patients. In general, the fall in blood chlorides was greater for the patients who showed diuresis. However, the greatest decrease (— 32 per cent) was found in patient 2, who did not show diuresis. The group of patients who showed diuresis exhibited an average total decrease of 10 per cent in blood chlorides. The group who showed no diuresis exhibited an average total decrease of only 3.5 per cent.

Uric Acid.—The uric acid of the urine and blood behaved similarly to the chlorides. When diuresis occurred, much greater quantities of uric acid were excreted in the urine (chart 2). This appeared to be purely a washing-out effect, since the concentration of uric acid in the urine was always decreased.

In all patients, except patient 7, the uric acid in the blood fell concurrently with the diuresis and the increased excretion of uric acid in the urine. In patient 7, there was an increase of 10 per cent in the uric acid in the blood in spite of a 20 per cent increase in total uric acid in the urine.

Blood Sugar.—No constant changes in blood sugar were demonstrable. The changes that did occur were small, did not seem to be affected by diuresis, and probably represented the range of experimental error or natural variations.

Pulse Rate.—Definite slowing of the pulse occurred in all subjects except patient 3, who was normal. The other two normal subjects (nos. 4 and 7) showed slowing of 10.5 and 15.8 per cent, respectively. The

greatest slowing (35 per cent) occurred in patient 12, whose heart was fibrillating. The other two patients with auricular fibrillation (nos. 8 and 10) also showed marked slowing of the pulse rate. Hence, the typical cardiac slowing of digitalis occurred in patients with normal and abnormal circulatory functions. The degree of cardiac slowing was less in those patients not showing diuresis (chart 2), but this difference might not be as marked in a larger number of patients. The greater slowing of those showing diuresis was related to circulatory abnormality of one sort or another.

CONCLUSIONS

1. The diuretic action of digitalis is variable, and practically limited to patients with edema of cardiac origin. The diuretic action in human subjects is accompanied by increases in the chloride and uric acid of the urine, and simultaneous decreases in the chloride and uric acid of the blood. In patients not showing increased diuresis, the metabolites of the blood and urine are unchanged or decreased.

Accordingly, the changes in these metabolites of the blood and urine following digitalis medication are mediated differently from those of the metallic and purine types of diuretics; there is a washing-out effect in the kidneys as the result of improvement in the general circulation, which increases renal filtration.

2. On the other hand, the diuresis of metallic and purine diuretics is characterized by simultaneous increases in the chlorides of the blood and urine, an action which is mediated, in part at least, by a direct tissue action of these diuretics and results in a mobilization of the chlorides of the tissues. The effect on metabolites in normal and edematous subjects is the same. This conclusion is based on previously published results.[5]

EXPERIMENTAL EDEMA PRODUCED BY PLASMA PROTEIN DEPLETION

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According to the conception advanced by Starling,[1] edema may be produced in at least two ways. The blood's capillary pressure (filtration force) may be increased while the plasma colloid osmotic pressure is kept constant, or the plasma colloid osmotic pressure may be lowered while the capillary pressure is kept constant. The rôle played by each of these two factors in fluid distribution has been the object of much investigation. The problem was first approached in our laboratory from the point of view of the capillary pressure change. It was found that acute rises in the arterial pressure (and hence in the capillary pressure) of cats and dogs were accompanied by increased concentration of their blood, the transudate being recovered in the tissues by analyses for water content.[2] Furthermore, direct measurements, in other laboratories, of capillary blood pressure and colloid osmotic pressure in human subjects have given quantitative meaning to the ideas of Starling, for it has been found that the average pressure in the capillaries of the human skin corresponds quite well with the osmotic pressure exerted by the plasma proteins.[3]

The application of the Starling conception of tissue fluid exchanges to explain the edema of nephrosis [4] attracted the interest of clinicians to the second factor mentioned, namely, the rôle played by the osmotic pressure of the plasma colloids in fluid distribution. Analyses performed on the blood of nephrotic [5] and undernourished [6] patients

From the Departments of Physiology and Pediatrics, School of Medicine and Dentistry, the University of Rochester.

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revealed consistently that the presence of edema was correlated with low plasma colloid osmotic pressures and low plasma protein concentrations.

At the same time the concentration of the plasma proteins was modified in mammals by experimental means. It was observed that edema developed in rats that were fed a diet low in protein.[7] The appearance of edema in such animals was found by later workers [8] to be directly related to the presence of low serum protein concentrations. The method of plasmapheresis [9] was utilized for reducing the plasma protein concentration of dogs, and the edema that resulted was concurrent with the development of low serum protein concentrations.[10] Both low serum protein concentrations and edema were also demonstrated in dogs that had been fed a diet low in protein.[10c]

Edema due to low serum protein concentrations has, therefore, been observed clinically and experimentally in a variety of conditions. Though the cause for the low serum protein concentration may differ, the end-result is the same—massive edema.

It is obvious that if no fluid were available for filtration, edema could not develop, even though the plasma proteins were below the so-called critical concentration. Experimental proof for this belief is contained in the protocols reported by some of the earlier workers who performed plasmapheresis, but who were not primarily interested in producing edema. Most of this literature [11] was found to be unsuitable for analysis from the point of view of the occurrence of edema, because of incomplete data, but some information was gleaned from the protocols of Kerr, Hurwitz and Whipple,[12] for in these experiments, in which body weight was used as an index, the absence of edema in hypoproteinic dogs was definitely associated with an inadequate intake of salt and water. Conversely, the occurrence of edema in these hypoproteinic dogs was, as far as could be ascertained, associated with the infusion of considerable quantities of fluid and salt. In the experiments

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10. (*a*) Leiter, L.: Proc. Soc. Exper. Biol. & Med. **26**:173, 1928; Experimental Nephrotic Edema, Arch. Int. Med. **48**:1 (July) 1931. (*b*) Barker, M. H., and Kirk, E. J.: Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, Arch. Int. Med. **45**:319 (March) 1930. (*c*) Shelburne, S. A., and Egloff, W. C.: Experimental Edema, Arch. Int. Med. **48**:51 (July) 1931.

11. (*a*) Abel, Rowntree and Turner (footnote 9). (*b*) Turner, B. B.; Marshall, E. K., Jr., and Lamson, P. D.: J. Pharmacol. & Exper. Therap. **7**:129, 1915. (*c*) Morawitz, P.: Beitr. z. chem. Phys. u. Path. **7**:153, 1906.

12. Kerr, W. J.; Hurwitz, S. H., and Whipple, G. H.: Am. J. Physiol. **47**: 356, 1918.

of other investigators,[10a,b] sodium chloride solution was supplied by stomach tube to the animals (a procedure not followed by the earliest workers in this field), and in this way a copious supply of salt and water for the development of the edema was insured, and the possibility remains that this supply of salt and water was chiefly responsible for the edema observed. The intake of water and food of their animals was not well controlled. The presence of edema was determined by their gross appearance and by an increase in body weight alone.

The obviously important rôle played by the intake of fluid and salt in the development of this type of edema suggested that a carefully controlled study of the water and chloride balances of hypoproteinic animals, supplemented by analyses of the chloride and water content of tissues obtained at autopsy, might be productive of interesting information.

TABLE 1.—*Diets Used in Experiments*

Substance	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Water, Gm.	Chloride, Gm.	Total, Gm.
Diet A						
Milk	21	25	32	560	0.68	638
Bread	17	1	102	70	1.15	191
Sugar	..	..	49	....	....	49
Totals	38	26	183	630	1.83	878
Diet B						
Same composition as that given, except that total quantity was one-half that of Diet A						

METHOD

Ten dogs were studied. They were fed a diet of known amount and composition (table 1) every twenty-four hours. These animals were kept in metabolism cages, and their daily intake of water and volume of urine were measured. They were weighed every day at approximately the same hour. Following a control period of from one to two weeks, they were subjected to plasma protein depletion by plasmapheresis.

Bleeding was performed without anesthesia, either from the femoral arteries or the jugular veins. The blood was drawn into a flask containing approximately 30 cc. of 3 per cent sodium citrate solution. From this blood the plasma was removed after centrifugation, and the cells were washed with isotonic sodium chloride solution and centrifugated. This process was repeated again, and finally, the cells, resuspended in calcium-free Locke's solution, were infused into the animal. Samples of arterial blood were removed and placed in bottles containing 0.02 Gm. of dried sodium oxalate for analysis. These specimens were taken immediately before the animal was bled and about ten minutes after the plasmapheresis was over. Sterile technic was employed in all but the first animal of this series.

The following analyses of the blood were performed during the control and experimental periods: plasma protein fractionation,[13] determination of the plasma

13. Wu, H., and Ling, S. M.: Chinese J. Physiol. **1**:161, 1927.

chloride,[14] hematocrit, determined on oxalated blood that had been placed in a capillary tube and centrifugated for ten minutes at the rate of 1,500 revolutions per minute, and the determination of nonprotein nitrogen.[15] Urinalysis on a twenty-four hour specimen included determinations of the volume, specific gravity, chloride [14] and total nitrogen,[15] and routine examinations for casts, albumin, etc.

At suitable points, the animals were killed by carbon monoxide gas, autopsy was immediately performed, and the tissues removed for sectioning and analyses of the water content and chloride. The water content of the tissues was determined in duplicate by drying previously weighed samples in an oven at from 90 to 100 C. until their weight checked within 0.2 per cent. Tissue chloride analyses were done, some in duplicate, on other weighed samples of moist tissue by the method of Van Slyke.[14]

EXPERIMENTS

In order to have some standard for comparing the water and chloride contents of the tissues of the experimental animals, it was thought best to establish control values from analyses of the tissues of control dogs which had been killed and on which autopsy had been performed, in the same manner as they had been established in hypoproteinic dogs. Hence one dog (357) that had been kept on the diet listed for three weeks and one (278) that had been taken directly from stock were killed, and their tissues analyzed and sectioned. Autopsy was also performed on a third dog (339) that had been subjected as a control measure to three bleedings and transfusions with defibrinated whole blood, and this animal was also included in this group. Table 2 contains the data obtained from the analyses on the three control animals.

The values obtained for the water content of the tissues agree quite closely with those of Engels,[16] as can be seen from table 3. A significant difference was found in these experiments between the water content of muscle from the limbs and that of muscle from the trunk. A higher average value for the water content of muscle of the limb was found than that reported by Engels. But the dogs used by Engels had probably been somewhat dehydrated, for they had been kept without food and water for four days before being killed.

The values for tissue chloride are also in good agreement with those reported by Damiens[17] and Cameron and Walton.[18] The percentage weights of the various organs and tissues were taken from the work of Sato [19] and Stewart.[20]

14. Van Slyke, D. D.: J. Biol. Chem. **58**:523, 1923.
15. Folin, O., and Denis, W.: J. Biol. Chem. **26**:473 and 491, 1916.
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18. Cameron, A. T., and Walton, C. H. A.: Tr. Roy. Soc. Canada (Sect. Biol. Sc.) **22**:1, 1928.
19. Sato, H.: Tohoku J. Exper. Med. **16**:487, 1930.
20. Stewart, G. N.: Am. J. Physiol. **58**:45, 1921.

TABLE 2.—*Analyses of Tissues of Control Dogs*

Tissue	Dog 357*		Dog 278†		Dog 339‡		Average Water Content, per Cent	Average Chloride Content, Millimols per 1,000 Gm. Tissue
	Per Cent Water Content	Chloride, Millimols per 1,000 Gm. Tissue	Per Cent Water Content	Chloride, Millimols per 1,000 Gm. Tissue	Per Cent Water Content	Chloride, Millimols per 1,000 Gm. Tissue		
Adrenal	61.80	33.5	63.10	27.5	66.35	23.1	63.75	28.0
Intestine	74.00	34.6	77.10	33.7	76.00	29.6	75.70	32.6
Kidneys	81.23	73.0	78.25	59.3	78.05	62.7	79.16	65.0
Liver	75.85	40.3	72.45	45.5	74.50	40.0	74.60	41.9
Lung	77.00	60.0	76.25	56.5	78.20	54.3	77.15	56.9
Pancreas	72.30	34.3	71.80	38.4	72.55	37.6	72.05	36.8
Spleen	77.70	40.9	76.80	39.8	77.75	41.3	77.42	40.7
Muscle								
Right fore leg	76.25	16.7	75.70	14.9	76.85	20.5	76.27	17.4
Left fore leg	76.80	16.6	76.35	15.5	77.00	19.1	76.71	17.1
Chest	72.80	12.8	71.50	13.9	73.15	....	72.50	13.4
Abdomen	74.35	16.5	70.10	15.1	72.85	....	72.40	15.8
Neck	73.85	15.4	.....	....	.....	....	73.85	15.4
Right upper hind leg	73.30	13.7	75.60	13.5	.....	13.7	75.78	13.6
Left upper hind leg	75.30	11.6	75.35	10.6	76.80	16.6	75.50	12.9
Right lower hind leg	75.00	10.9	74.25	14.9	77.60	13.6	75.62	13.1
Left lower hind leg	76.20	14.1	73.10	12.3	77.30	19.9	75.53	15.4
Skin								
Right fore leg	62.45	51.2	59.95	63.9	69.10	67.5	63.83	60.9
Left fore leg	64.00	55.2	64.85	65.3	67.85	67.9	65.57	62.8
Abdomen	56.60	43.7	53.50	39.6	61.25	45.3	57.12	42.8
Neck	48.40	32.3	.....	....	.....	....	.....	....
Chest	57.20	42.7	41.30	41.1	60.00	56.4	52.80	46.7
Right upper hind leg	60.35	43.2	53.75	40.7	58.25	63.7	57.65	49.2
Left upper hind leg	51.45	41.2	44.00	39.7	65.95	63.5	53.80	48.1
Right lower hind leg	62.15	53.3	59.25	57.0	66.40	61.5	62.57	57.3
Left lower hind leg	51.10	54.0	50.20	58.0	67.10	62.5	56.10	58.2

* Dog 357 was kept on diet A for three weeks.

† Dog 278 was kept on diet A for three weeks, and subjected to three bleedings followed by infusions of whole defibrinated blood.

‡ Dog 339 was taken from stock and immediately killed.

TABLE 3.—*Average Values for Tissue Chloride and Water Content*

Tissue	Per Cent Water Content		Chloride Content, Millimols per 1,000 Gm. Tissue			Per Cent Weight of Tissue
	Engels	Author	Damiens	Cameron and Walton	Author	Stewart and Sato
Adrenal	.....	63.75	52.20	35.00	28.03	0.0121
Intestine	75.40	75.70	.....	37.20	32.63	6.50
Kidney	76.72	79.16	63.10	70.70	65.00	0.57
Liver	73.70	74.60	33.00	38.40	41.90	2.90
Lung	78.70	77.15	67.50	64.80	56.90	0.83
Pancreas	.....	72.05	.....	38.80	36.80	0.22
Spleen	78.60	77.42	50.40	48.20	40.70	0.28
Muscle						
A (Limb)	73.50	75.90	20.30	18.90	14.93	42.84
B (Trunk)	.....	72.92	.....	.....	14.58	.....
Skin	58.90	58.70	.....	.....	53.30	16.11

The protocols of the most significant experiments are shown. Each of these protocols, although similar to the others in its major features, contains details that are important enough to justify their presentation in full.

PROTOCOLS OF EXPERIMENTS

PROTOCOL 1 (*dog 133, female pointer*).—Four hundred cubic centimeters of this dog's blood was deprived of plasma every other day for forty-six days. Diet A was fed. At no time was an increase in body weight recorded. On the contrary, there was a gradual loss in body weight, while the serum protein level was kept quite constantly between 5 and 5.5 per cent despite the plasmaphereses (fig. 1). This might indicate that the animal replaced its serum protein at the expense of its body protein.

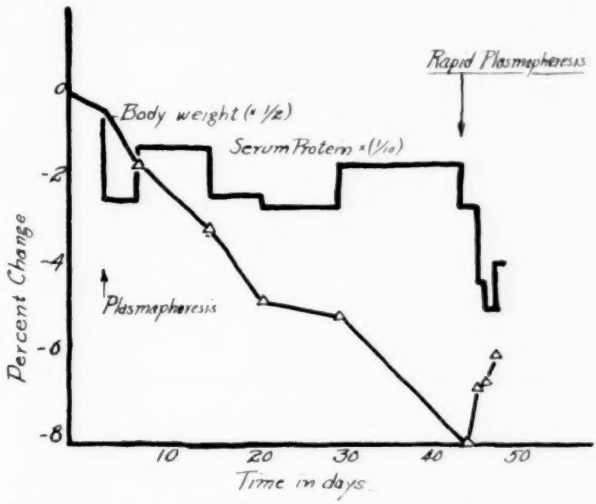

Fig. 1 (dog 133).—Changes in the serum protein and body weight.

TABLE 4.—*Changes in the Serum Protein and Body Weight of Dog 133*

Date	Body Weight, Kg.	Serum Proteins, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.	Albumin Globulin Ratio	Water Intake, Cc.	Cc. of Blood Subjected to Plasmapheresis
3/ 7	19.20	7.23	....	....	....	1,046	...
3/11	19.07	5.53	3.48	2.05	1.70	901	...
3/15	18.55	6.37	4.08	2.29	1.78	1,077	...
3/30	18.04	5.56	3.32	2.24	1.48	1,360	...
4/ 3	17.40	5.35	3.42	1.93	1.77	895	...
4/12	17.28	6.10	3.86	2.24	1.72	710	...
4/27	16.04	5.40	....	....	....	880	...
4/28	16.57	4.35	2.60	1.75	1.48	1,270	400
		3.94	2.36	1.58	1.50	.....	400
4/29	16.71	4.40	2.46	1.94	1.27	1,100	400
		3.02	1.62	1.40	1.40	.....	250
4/30	17.00	4.47	2.57	1.90	1.35	1,220	350

Beginning on the forty-seventh day, rapid plasmapheresis was performed, as indicated in table 4. Edema appeared when the serum proteins had fallen to an average level of 4.19 per cent. The appearance of the edema was associated with an increased intake of water. The edema appeared grossly to be confined to the hind legs, which exhibited the pitting typical of this condition when pressure was applied.

Autopsy was performed, and the results of the tissue analyses are contained in table 5. The tissues of the hind legs were not analyzed in this dog, but they appeared to be more highly hydrated than those of the fore legs. However, these analyses accounted for only 30 per cent of the hydration observed by measurements

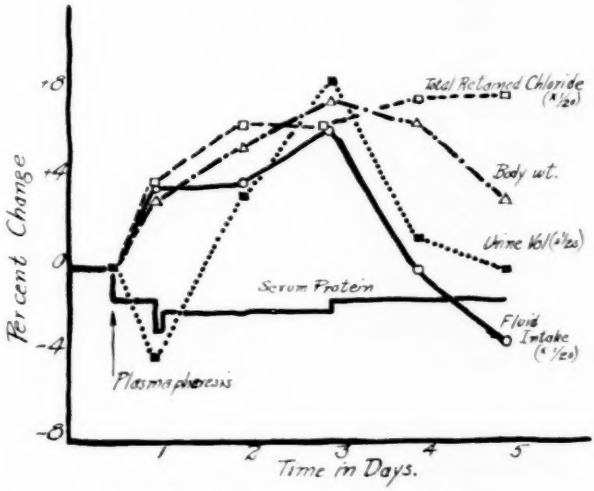

Fig. 2 (dog 285).—Water and chloride balance.

TABLE 5.—*Water Content of the Tissues of Dog 133*

Tissue	Per Cent Water Content	Excess Water Gm. per 1,000 Gm. Tissue
Liver	79.70	51.0
Kidneys	83.85	46.9
Spleen	79.20	18.8
Muscle		
Left fore leg	77.85	19.5
Right fore leg	77.25	13.5
Abdomen	77.55	46.3
Chest	75.30	29.8

of weight. For this reason it was thought advisable on later dogs to perform complete analyses of tissues, including the skin and the muscles of the hind legs.

PROTOCOL 2 (*dog 285, male setter*).—Plasmapheresis was performed as indicated in table 6, aseptic precautions being employed. Edema appeared after the first day of plasmapheresis with the serum proteins at a level of 4 per cent. The development of the edema was associated with a retention of chloride (stored isotonically

at the start) and an increased intake of water. The partial disappearance of the edema was associated with a rise in the serum proteins to 4.8 per cent, and a great decrease in the intake of water and an increased output of urinary chloride (fig. 2 and table 7).

It can be seen from the urinary specific gravity that the urine of the dog in the edematous state was more dilute than his control urine. This may have been due to the fact that the lowered colloid osmotic pressure of the plasma prevented

TABLE 6.—*Blood Changes of Dog 285*

Day	Serum Protein, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.	Albumin Globulin Ratio	Fibrinogen, Gm. per 100 Cc.	Hematocrit	Plasma Chloride, Millimols per 1,000 Cc.	Plasma Non-protein Nitrogen, Mg. per 100 Cc.	Cc. of Blood Subjected to Plasmapheresis
Control	7.06	4.60	2.46	1.87	0.24	49.0	103.8	35.8	...
1st*	4.53	3.11	1.42	2.19	0.15	31.0	124.2	....	300
									350
2nd	4.98	3.57	1.41	2.53	0.34	35.9	.....	33.4	450
*	3.05	2.28	0.77	2.96	0.19	31.0	124.3	....	450
3rd	5.06	3.77	1.29	2.92	0.57	38.3	103.8	....	...
*	3.26	2.09	1.17	1.79	0.24	23.5	120.0	26.8	450
4th	4.78	3.03	1.75	1.73	0.43	25.0	112.0	25.0	400
*	3.47	2.03	1.44	1.41	0.28	21.7	120.0	21.7	350
									400
5th	5.00	3.04	2.05	1.48	0.47	21.8	.....	....	
*	4.34	2.82	1.52	1.86	0.13	....	124.3	29.6	250
6th	5.27	3.04	2.23	1.36	0.34	17.0	.....	....	200
*	3.68	2.42	1.26	1.92	0.30	17.2	120.0	....	250

* Analyses made on samples taken ten minutes after last plasmapheresis.

TABLE 7.—*Water and Chloride Metabolism of Dog 285*

Day	Water Intake, Cc.	Urine Volume, Cc.	Body Weight, Kg.	Urine, Specific Gravity	Urine Nitrogen, Gm.	Urine Chloride, Millimols	Food Chloride, Millimols	Locke's Chloride,* Millimols	Total Chloride, Millimols	Retained Chloride, Millimols
Control	694	360	15.80	1.025	4.3	53.8	51.7	.....	51.70	....
1	1,216	50	16.28	.....	1.1	4.3	51.7	30.10	81.80	77.5
2	1,231	500	16.70	1.013	3.5	30.7	51.7	30.10	81.80	51.1
3	1,626	965	17.00	1.014	8.7	70.0	51.7	24.50	76.20	6.2
4	672	470	16.80	1.017	6.6	23.9	29.0	12.15	41.15	17.2
5	200	355	16.20	1.023	5.3	12.8	....	17.95	17.95	5.1

* Locke's solution contains a higher concentration of chloride than does dog plasma. The correction for the extra chloride introduced into the dog by this means was made by multiplying the difference between the plasma chloride level before and after plasmapheresis by the estimated plasma volume.

absorption of water from the kidney tubules at as rapid a rate as in the normal animal. It is also conceivable that filtration of saline through the glomerulus was increased because of the inability of the plasma to retain the fluid supplied to it.

The results of the tissue analyses shown in table 8 demonstrate that the retention of chloride indicated by the urinalyses was substantiated by the recovery of the stored chloride in the tissues. It is also apparent from these tissue analyses that the edema was widely distributed and prevailed in visceral organs as well as in skin and muscle.

TABLE 8.—*Content of Tissue Chloride and Water of Dog 285*

Tissue	Per Cent Water Content	Chloride Content, Millimols per 1,000 Gm. Tissue	Excess Water, Cc. per 1,000 Gm. Tissue	Excess Chloride, Millimols per 1,000 Gm. Tissue	Molarity of Stored Chloride
Adrenal	76.70	38.40	129.5	+10.37	0.125
Intestine	81.75	47.00	60.5	+14.37	0.422
Kidneys	79.20	47.90	.....	—17.10	.....
Liver	73.90	38.10	.....	— 3.80	.....
Lung	80.45	50.60	33.0	+ 2.70	0.122
Pancreas	78.40	44.70	68.5	+ 7.90	0.124
Spleen	78.70	29.50	.....	—11.20	.....
Muscle					
Right fore leg	77.70	21.80	18.0	+ 6.87	0.582
Left fore leg	76.80	23.00	9.0	+ 8.07	0.897
Right upper fore leg	74.60	21.90	16.8	+ 7.32	0.436
Left upper fore leg	76.90	19.80	39.8	+ 5.22	0.131
Chest	73.40	19.60	4.8	+ 5.02	0.105
Right upper hind leg	77.30	24.90	14.0	+ 9.97	0.712
Left upper hind leg	77.95	23.20	20.5	+ 8.27	0.248
Right lower hind leg	77.60	23.40	17.0	+ 8.47	0.201
Left lower hind leg	78.10	23.80	22.0	+ 8.87	0.248
Skin					
Fore leg	69.50	54.60	108.0	+16.20	0.150
Chest	69.85	55.60	111.5	+ 2.30	0.021
Abdomen	66.55	54.20	78.5	+ 0.90	0.012
Upper hind leg	71.70	79.30	130.0	+26.00	0.200
Lower hind leg	81.30	71.00	226.0	+17.70	0.078

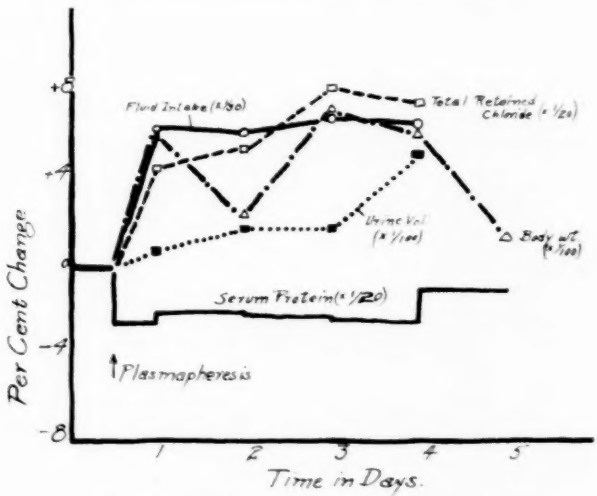

Fig. 3 (dog 346).—Water and chloride balance.

PROTOCOL 3 (*dog 346, male setter*).—The data of this experiment are contained in figure 3 and tables 10 and 11. This dog was given in addition to diet B, 1,000 cc. of 0.9 per cent sodium chloride solution every day by stomach tube, in order to provide a copious supply of salt and water, and was subjected to plasmapheresis, as indicated in table 11. The total protein levels (table 11) were probably not

TABLE 9.—*Distribution and Recovery of Chloride and Water in Tissues of Edematous Dogs*

	Dog 31-2			Dog 285			Dog 286	
	Muscle	Skin	Organs	Muscle	Skin	Organs	Muscle	Skin
Chloride recovered (millimols)	79.90	17.60	7.40	51.20	32.56	13.98	45.99	38.30
Water recovered (Gm.)	95.70	228.00	20.90	122.00	334.00	6.76	63.50	196.50
Concentration of chloride recovered (millimols)	0.953	0.167	.....	0.384	0.092	.....	0.558	0.142
Per cent chloride recovered	76.10	16.70	7.05	52.30	33.30	14.30	54.60	45.40
Per cent water recovered	30.80	62.40	6.80	30.50	67.20	2.35	30.80	69.20
Total chloride recovered (millimols)		104.90			97.74			84.29
Total chloride retained (millimols)		142.80			157.22			88.30
Per cent total retained chloride recovered		73.50			62.00			95.50
Total water recovered (Gm.)		323.70			456.03			260.00
Total water retained (Gm.)		940.00			400.00			258.00

TABLE 10.—*Water and Chloride Metabolism*

Day	Water Intake, Cc.	Urine Volume, Cc.	Body Weight, Kg.	Urine Specific Gravity	Urine Nitrogen, Gm.	Urine Chloride, Millimols	Ingested Chloride, Millimols	Locke's Chloride, Millimols	Total Chloride, Millimols	Retained Chloride, Millimols
Dog 346										
Control	465	335	10.98	1.022	5.2	28.2	25.7	.....	25.7	.....
1st	1,355	600	11.64	1.016	2.5	102.5	179.5	145.0	194.0	91.5
2nd	1,375	950	11.25	1.020	3.3	175.7	179.5	137.0	193.2	17.5
3rd	1,465	925	11.79	1.014	4.6	143.5	179.5	181.5	197.7	54.2
4th	1,350	2,050	11.55	1.010	4.6	304.2	162.5	171.0	179.6	—124.6
5th	.....	.....	11.14	.....	...	.....	.....	.....	.....	.....
Dog 31-2										
Control	741	300	11.00	1.025	...	49.6	51.3	.....	51.3	1.7
1st	4,200	3,200	11.94	1.010	...	497.0	621.0	17.1	638.1	141.1
Dog 286										
Control	700	300	14.41	1.024	6.1	52.4	51.3	.....	51.3	.....
1st	2,630	1,435	14.33	1.025	5.7	188.0	205.8	.....	205.8	17.8
2nd	2,460	1,100	.....	1.020	4.7	142.0	205.8	.....	205.8	63.8
3rd	2,455	1,335	15.10	1.014	7.3	184.5	205.8	.....	205.8	21.3
4th	2,430	1,380	14.35	1.011	5.2	210.0	205.8	.....	205.8	—4.2
5th	2,230	1,220	14.51	1.015	5.2	188.0	205.8	.....	205.8	17.8
6th	3,080	2,000	15.00	1.008	...	304.0	321.8	.....	321.8	17.8
7th	2,430	1,630	14.65	1.012	...	251.8	205.8	.....	205.8	—46.0

TABLE 11.—*Changes in the Blood*

Day	Serum Protein, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.	Albumin Globulin Ratio	Fibrinogen, Gm. per 100 Cc.	Hematocrit	Plasma Chloride, Millimols per 1,000 Cc.	Plasma Nonprotein Nitrogen, Mg. per 100 Cc.	Cc. of Blood Subjected to Plasmapheresis
Dog 346									
Control	7.34	.....	.....	.....	0.50	37.7	120.0	31.0	200
1st	3.60	2.40	1.20	2.00	0.43	49.3	124.2	24.0	...
2nd	4.70	2.59	1.91	1.36	.....	34.3	108.0	.....	200
3rd	3.88	2.74	1.14	2.40	0.43	19.0	124.2	.....	350
4th	3.65	2.45	1.20	2.02	0.65	10.0	128.0	.....	350
5th	3.16	2.45	0.71	3.45	0.86	10.0	124.2	.....	200
6th	5.99	2.99	3.00	1.00	0.54	.....	.....	.....	...
Dog 31-2									
Control	6.12	4.13	1.99	2.06	.....	38.0	95.0	.....	275
After plasmapheresis	3.49	.....	.....	.....	.....	.....	.....	.....	275
1st day	4.43	2.72	1.73	1.59	.....	41.2	91.7	38.0	...

representative of the true levels for the entire twenty-four hours, for they were obtained from analyses of samples taken immediately after plasmapheresis. From this protocol it is apparent that the edema can be obtained very quickly if enough fluid and salt are made available for storage.

The tissue analyses performed on this dog were made of doubtful value by the fact that shortly before autopsy was performed, the animal was given 2 liters of isotonic sodium chloride solution by stomach tube.

TABLE 12.—*Content of Tissue Chloride and Water of Dog 31-2*

Tissue	Per Cent Water Content	Chloride, Content, Millimols per 1,000 Gm. Tissue	Excess Water, Cc. per 1,000 Gm. Tissue	Excess Chloride, Millimols per 1,000 Gm. Tissue	Molarity of Stored Chloride
Adrenal	61.90	27.7	....	— 0.26	.....
Intestine	78.40	34.3	27.0	+ 1.67	0.062
Kidneys	80.05	69.9	8.9	+ 4.90	0.552
Liver	76.40	46.8	18.0	+ 4.90	0.273
Lung	80.10	70.0	29.5	+13.10	0.444
Pancreas	77.80	40.8	57.5	+ 4.00	0.070
Spleen	78.55	41.5	11.3	+ 0.80	0.071
Muscle					
Right upper fore leg	77.05	28.3	11.5	+13.37	1.160
Left upper fore leg	76.35	24.9	4.5	+ 9.97	2.220
Neck	71.85	27.1	....	+12.52	.....
Chest	72.10	32.7	....	+18.12	.....
Abdomen	73.90	25.3	9.8	+10.72	1.090
Right upper hind leg	80.40	45.7	45.0	+30.77	0.683
Left upper hind leg	80.40	30.5	45.0	+15.57	0.346
Right lower hind leg	80.50	35.3	46.0	+20.37	0.442
Left lower hind leg	78.10	33.2	22.0	+18.27	0.830
Skin					
Right lower fore leg	70.85	71.6	121.5	+15.60	0.128
Left lower fore leg	68.45	77.3	97.5	+21.20	0.218
Neck	31.15	41.8	.....	— 2.99	.....
Chest	47.80	48.6	.....	+ 3.81	.....
Abdomen	56.40	50.4	.....	+ 5.61	.....
Right upper hind leg	80.65	67.7	219.5	+11.60	0.053
Left upper hind leg	83.00	48.5	243.0	— 7.60	.....
Right lower hind leg	88.45	55.6	297.5	+ 2.30	0.007
Left lower hind leg	81.40	....	227.0	.....	.....

PROTOCOL 4 (*dog 31-2, male collie*).—This dog was subjected to plasmapheresis twice in one day, as indicated in table 11, and was given a total of 3,700 cc. of isotonic sodium chloride solution by stomach tube. Three hours after the completion of the plasmaphereses, distinct pitting edema of the hind legs was observed. Six hours after plasmapheresis, a puncture was made through the pendulous skin of the right thigh. Fluid obtained from this site contained 0.3 per cent of protein by Kjeldahl analysis and 115 millimols of chloride per thousand cubic centimeters (0.67 per cent sodium chloride). The albumin-globulin ratio of this fluid was 9.05, indicating that it was mostly albumin. Sixteen hours after plasmapheresis, the animal was killed, and tissues were removed for analysis. There was considerable pleural and peritoneal fluid. The ascitic fluid contained 0.51 per cent of protein by Kjeldahl analysis. Its albumin-globulin ratio was 12.6, and its chloride

content was 116 millimols per thousand cubic centimeters. The plasma chloride value was 91.7 millimols per thousand cubic centimeters, i. e., lower than the chloride content of the edema fluid, indicating the rôle of the Donnan equilibrium in the distribution of this ion.

The edema was definitely shown by the tissue analyses (table 12) to be most patent in the limbs and the visceral organs. The upper abdominal, thoracic and neck tissues showed little hydration.

The data from this particular animal are especially decisive in fitting the Starling hypothesis. This is apparently the first instance to be reported in which edema occurred so quickly and in which its appearance was substantiated by tissue analyses. These data also clearly demonstrate the important rôle played by the intake of fluid and sodium chloride in the development of the edema.

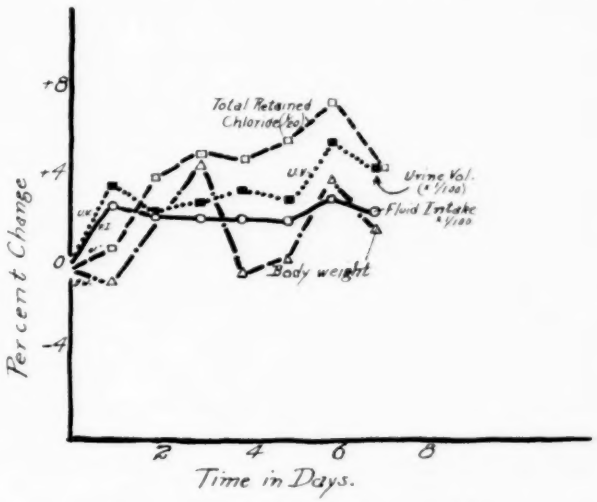

Fig. 4 (dog 286).—Water and chloride balance.

Given the low plasma colloid osmotic pressure, the speed of development of the edema, therefore, depends on the rapidity with which water and sodium chloride are made available for storage. There is considerable evidence to show that edema may be produced in normal human subjects merely by the ingestion of adequate amounts of isotonic sodium chloride solution.[21] The presence of a low plasma protein concentration would facilitate the appearance of such an edema.

Protocol 5 (*dog 286, male airedale*).—This dog was not subjected to plasmapheresis, and consequently the serum protein level was quite constantly about 7 per cent. It was fed diet A and was also given 1,000 cc. of 0.9 per cent sodium chloride solution by stomach tube daily for a period of six days. Although this animal eliminated most of the ingested chloride, it still retained a definite quantity of chloride and water. The chloride and water were recovered by the tissue analyses as shown in table 13.

21. Baird, M. M., and Haldane, J. B. S.: J. Physiol. **56**:259, 1922.

TABLE 13.—*Content of Tissue Chloride and Water of Dog 286*

Tissue	Per Cent Water Content	Chloride, Content, Millimols per 1,000 Gm. Tissue	Excess Water, Cc. per 1,000 Gm. Tissue	Excess Chloride, Millimols per 1,000 Gm. Tissue	Molarity of Stored Chloride
Adrenal	65.00	26.4	12.5	.....	.....
Intestine	77.50	35.6	18.0	+ 2.97	0.165
Kidneys	77.60	53.2	....	.....	.....
Liver	73.30	44.5	....	+ 2.60	.....
Lung	.....	....	....	.....	.....
Pancreas	72.05	36.3	....	.....	.....
Spleen	77.50	40.7	....	.....	.....
Muscle					
Right fore leg	78.80	39.6	29.0	+24.67	0.850
Left fore leg	78.00	29.9	21.0	+14.97	0.713
Neck	75.80	23.4	28.8	+ 8.47	0.294
Chest	75.50	....	25.8	.....	.....
Abdomen	75.10	26.2	21.8	+11.27	0.517
Right upper hind leg	76.35	17.0	4.5	+ 2.07	0.460
Left upper hind leg	75.60	12.4	....	.....	.....
Right lower hind leg	76.40	17.5	5.0	+ 2.57	0.512
Left lower hind leg	75.60	17.0	.....	+ 2.07	.....
Skin					
Right fore leg	70.80	80.0	121.0	+21.30	0.176
Left fore leg	70.55	78.8	118.5	+20.10	0.170
Neck	69.40	73.4	107.0	+14.70	0.137
Chest	69.50	73.0	108.0	+14.30	0.132
Abdomen	70.65	69.4	119.5	+13.70	0.115
Right upper hind leg	71.95	78.2	132.5	+19.50	0.147
Left upper hind leg	70.60	76.5	119.0	+17.80	0.150
Right lower hind leg	75.85	72.7	171.5	+14.00	0.082
Left lower hind leg	70.00	77.2	113.0	+18.50	0.164

From a consideration of the data from this experiment, it is apparent that there is a definite similarity between the process of salt and water storage in this animal and in the hypoproteinic dogs.

COMMENT

1. *Total Protein.*—Edema occurred in the dogs when the serum protein level was about 4 per cent.

2. *Albumin-Globulin Ratio.*—It can be seen from protocol 1 that when plasmapheresis was performed over a long period of time, comparatively small percentages of the total blood volume of the dogs being bled at one time, the albumin-globulin ratio was lowered. There was no massive albuminuria in this animal that could have accounted for this lowering of the ratio. These data may be taken as evidence for the fact that under the particular conditions stated in this protocol, the globulin fraction is restored faster than the albumin fraction. This confirms the work of Kerr, Hurwitz and Whipple.[12]

The dogs reported in protocols 2, 3 and 4 were subjected to a type of plasmapheresis that was intermediate between the "rapid" and the "slow" plasmapheresis performed by Whipple and his co-workers.[22] The resultant albumin-globulin ratios were also a mixture of the two types of results reported by these investigators. Whipple and his

22. Kerr, Hurwitz and Whipple (footnote 12). Smith, H. P.; Belt, A. E., and Whipple, G. H.: Am. J. Physiol. **52**:54, 1920.

co-workers [12] reported a lowering and even a reversal in the albumin-globulin ratio after slow plasmapheresis. It is evident from the protocols on the regeneration of the plasma proteins after rapid depletion [23] that, after moderately great amounts of plasmapheresis, the albumin fraction is restored more quickly than the globulin. It was found in our dogs that, during the first day or so, the albumin fraction was restored more rapidly than the globulin fraction. Later, the globulin fraction was replaced more rapidly.

Albumin-globulin ratios were also determined immediately before and ten minutes after plasmapheresis. It was consistently found by these analyses that the albumin fraction was replaced more rapidly than the globulin. This evidence confirms the observations of a number of workers.[24]

The cause for the early restoration of the albumin fraction is not very clear. It may be that there is a good reserve store of it available. Drinker [23] has presented some evidence on this point. He believes that the emergency restoration of plasma protein immediately after plasmapheresis is made at the expense of the lymph. He finds high albumin-globulin ratios for lymph and believes that the influx of lymph and tissue fluid into the blood is one of the reasons for the rise in the albumin fraction immediately after plasmapheresis.

The objections that can be raised against any method which arbitrarily divides the serum proteins into only two groups should be kept in mind in considering these data on albumin-globulin ratios.

3. *Fibrinogen.*—This protein was replaced with extreme rapidity after plasmapheresis, and in many instances tended to reach values decidedly above the control figures, regardless of the fact that the other plasma proteins were at very low levels. A similar reaction of fibrinogen to plasmapheresis was observed by Smith, Belt and Whipple.[25]

4. *Red Corpuscles.*—There was a gradual fall in the hematocrit in most of the experiments that were performed. No attempt was made to remedy this by a transfusion of blood from another animal. The reason for the destruction of the red cells (which in dog 285 was accompanied by hemoglobinuria) is not definitely known. However, a good portion of the red cell loss was probably due to hemolysis promoted by an increase in fragility of the cells caused by the mechanical violence to the cells during the process of plasmapheresis.

It may be claimed that the anemia indicated by the low hematocrit values, or the resulting poor oxygen supply to the tissues, was a primary

23. Loewen, D. F.; Field, M. E., and Drinker, C. K.: Am. J. Physiol. **98**:70, 1931.

24. Morawitz, P.: Beitr. z. chem. Phys. u. Path. **7**:153, 1906. Loewen, Field and Drinker (footnote 23).

25. Smith, Belt and Whipple (footnote 22).

factor in the production of these edemas. However, the recovery of transudates low in protein content and the results of various control procedures would indicate that these factors were not the major ones.

5. *Water in the Tissues.*—The data obtained from all of the tissue analyses have been summarized in table 9. The comments cited are based on this table.

The edema has been described on the basis of gross observation as being localized more or less in the hind portion of the animals with little or no involvement of the fore legs.[10a] The inadequacy of conclusions drawn in this manner are evident from the analyses of the tissues that were performed. These show that the edema is more widely distributed than has been reported. Appearances to the contrary, the fore legs are overhydrated, although not to as great a degree as the hind legs. It is interesting to observe that although both the muscle of the hind limbs and that of the fore limbs are involved in this edema, the upper abdominal, thoracic and neck muscle usually exhibit normal water contents. Skin, as shown by the analyses, is quite uniformly hydrated all over the body, although the tendency is for it to be slightly more hydrated in the region of the hind legs. The analyses of the visceral organs show that these tissues are considerably hydrated. It is interesting to speculate as to the factors concerned in the distribution of this edema. In the Starling conception, two factors that probably are quite uniform all over the body at any one moment are the tissue colloid osmotic pressure and the plasma colloid osmotic pressure. The factor that may then be considered as the variable is the effective hydrostatic pressure in the capillaries. There are, of course, differences in the absolute capillary pressures in the different regions of the body. However, these differences are not the only ones. One tissue may be unable to expand as much as another because of the binding force exerted by cell membranes or enveloping sheaths, etc. This extra force prevents the tissue from swelling to its fullest extent and thereby eventually opposes the capillary filtration pressure. It is, therefore, suggested that in applying the Starling hypothesis, besides considering the factors of capillary pressure and plasma colloid osmotic pressure and extracapillary colloid osmotic pressure (which is presumed to remain constant throughout one of our experiments), the, at present, unmeasured force of tissue turgor or pressure should be recognized as being of definite importance in this system. "Tissue pressure" has been recognized by Landerer [26] and Krogh [27] as an important element in the maintenance of the water equilibrium of the tissues. The tendency for edema fluid to accumu-

26. Landerer, A. S.: Die Gewebsspannung in ihrem Einfluss auf die örtliche Blut- und Lymphbewegung, Leipzig, J. C. W. Vogel, 1884.

27. Krogh (footnote 5, p. 304).

late in the serous cavities and in "soft" tissues (e. g., the eyelids) may be due to the ability of these tissues to increase in volume without changing their tensions appreciably.

Differences in the ability of protein to pass out of the blood in the different regions may explain in part the distribution of the edema. However, these differences are probably at a minimum following plasmapheresis, for several mechanisms are present which tend to raise the serum protein level, possibly at the expense of the protein of the tissue fluid.

The data from the organ analyses are, so far as can be ascertained, the first to show where edema fluids are deposited. It appears important to us to know definitely that this edema involves visceral organs as well as other tissues. There is pulmonary edema in these animals. The pancreas in all of the edematous dogs ranged from 5.5 to 10 per cent overhydrated. In the protocols of Whipple, Smith and Belt [25] there were several instances in which pancreatic edema was noted after plasmapheresis, while gross general edema was not noted.

The tissue analyses reported from this investigation do not by any means represent the extremes to which this edema may develop. In fact, the changes reported may be regarded as being only moderate ones which could have been accentuated by prolonging the experimental period.

6. *Tissue Chloride.*—The tissue chloride data confirm the data on chloride balance of the dog as a whole by showing that there is a definite chloride storage in all of the analyzed tissues. It can be seen from table 9 that 61 per cent of the recovered chloride was found in muscle where it was stored hypertonically, while 66 per cent of the recovered water was found in the skin. The extra chloride in the skin appeared to be stored isotonically.

In considering the distribution of water and chloride in the edematous tissues, we should remember that normally the skin has a low water content and a high chloride content. Muscle, on the other hand, has normally a high water content and a low chloride content. It may be that these properties are vitally concerned in deciding which of the tissues shall store more water and which shall store more chloride.

7. *Water and Chloride Metabolism.*—All but a negligible amount of the ingested chloride of these animals was sodium chloride. However, how much of the urinary or tissue chloride was accompanied by sodium is not known, but most of the changes found were probably changes in sodium chloride metabolism. The experiments demonstrate that definite retentions of chloride and water are associated with the appearance of the edema. The lowering in the serum protein permits the escape

of water and salt whenever the supply of these materials is adequate. At no time is water stored by these animals without some chloride being simultaneously retained.

If the isotonic sodium chloride solution is not supplied to the dog by stomach tube, the animal retains some chloride and ingested water from the food and Locke's solution, storing the combination isotonically. Data on the body weight seem to indicate that the retained chloride is stored isotonically by the body as a whole, but that the chloride is recovered in isotonic proportions in skin and in hypertonic concentrations in muscle.

The abatement of the edema is definitely associated with a rise in the serum proteins and is accompanied by a diuresis, an increased excretion of chloride and a decrease in the intake of fluid. In some cases, the diuresis is a water diuresis, and little of the stored chloride is eliminated. It has been claimed, therefore, that the kidney in this condition cannot eliminate chloride as well as the kidney of a normal dog. However, we have definite evidence for the fact that the chloride excreting power of the edematous animals is quite normal. The dogs of protocols 2, 3 and 4 were given great amounts of chloride, and they succeeded in eliminating amounts of it that were far above the control excretions of chloride. It can be said, therefore, that probably a good portion of the chloride in the edematous dog gets into the tissues before it can be excreted by the kidneys. The fact that chloride does not accompany the water in all instances when diuresis occurs is no proof of damaged kidney excreting power for chloride. It may be that here again, the tissues hold on to the chloride tenaciously so that it is not offered to the kidney for excretion.

Dog 286, as was stated, had been given 1,000 cc. of 0.9 per cent sodium chloride solution by stomach tube for a week and had then been killed and autopsy performed. The tissue analyses revealed the fact that this dog was slightly overhydrated and had retained some chloride in its tissues, regardless of the fact that its plasma proteins were at the normal level, for this animal had at no time been subjected to plasmapheresis. Retention and storage of chloride after ingestion of sodium chloride by normal dogs has been reported consistently by Engels [16] and and Wahlgren [28] and others.

The similarity between the results of the tissue analyses of this dog and those of the hypoproteinic ones suggests that low serum protein edema in dogs is a sodium chloride edema that has reached extreme proportions because of the lowered plasma colloid osmotic pressure which facilitates filtration of fluid into the tissues.

28. Wahlgren, V.: Arch. f. exper. Path. u. Pharmakol. **61**:97, 1909.

Restriction of the fluid and salt of the diet has been advocated for years in the treatment of edema in human patients.[29] These experiments justify the employment of such measures in the management of the edemas of nephrosis, malnutrition and other conditions in which low serum protein concentrations occur.

CONCLUSION

A study was made of the water and chloride metabolism of normal dogs and of dogs that had been rendered hypoproteinic by plasmapheresis. The sites of deposition of water and chloride were ascertained by tissue analyses.

On the basis of the data obtained, it is concluded that the edema that occurs in dogs rendered hypoproteinic by plasmapheresis is a sodium chloride edema, the development of which can be hastened by increasing the intake of fluid and sodium chloride of these animals.

The sound advice and encouragement rendered by Dr. E. F. Adolph and Dr. S. W. Clausen were of inestimable value in the initiation and consummation of these experiments.

29. Widal, F., and Javal, A.: J. de physiol. et de path. gén. **5**:1107 and 1123, 1903.

Book Reviews

The Rheumatic Infection in Childhood. By Leonard Findlay, M.D., D.Sc., M.R.C.P., Visiting Physician, East London Hospital for Children, Shadwell; Honorary Member, American Pediatric Society; Honorary Member, Canadian Pediatric Society; Honorary Fellow, Medical Society, Budapest; Honorary Member, Interstate Medical Association, North America; Formerly Professor of Pediatrics, Glasgow University, and Director of Child Welfare, League of the Red Cross Societies, Geneva. First edition. Cloth. Price, $3.50. Pp. 179, with charts and illustrations. New York: William Wood & Company, 1932.

On reading this book one is further impressed with the immense amount of work that has been done in this field. The book consists of a critical analysis of 701 cases of rheumatic infection that have come under the author's observation during the past sixteen years. While the book contains nothing that is essentially new, the facts obtained from the study are well organized and presented and form a definite addition to the existing material. One realizes that the study of even so large a series as 701 cases does not tell the story of rheumatic infection. It tells only the story of rheumatic infection in one locality, studied by one observer or group of observers. Consequently, the opinions formed from the study of this group will not go altogether unchallenged.

In this series of 701 cases there was a total of 489 cases of heart disease. Other authors have found the incidence of heart disease a bit higher. One wonders whether the author's diagnostic criteria would correspond to those generally accepted. He speaks of a purulent effusion about the joints in certain cases. Many observers will not admit that a suppurative arthritis falls within the group generally accepted as acute rheumatic fever.

The author is not convinced that the Aschoff body is the typical lesion of rheumatic heart disease; much less does he favor the notion that this lesion occurs elsewhere as a result of rheumatic infection. He states that he has never had demonstrated to him an Aschoff body in the heart of a child who has been under his observation. He explains the round cell infiltration as the result of disintegration of muscle. He does not state the number of cases that were subjected to histologic study, and there were postmortem studies in only 37 cases, not a great number.

A considerable portion of the book is devoted to a discussion of valve disease, its incidence and prognostic value. An attempt is made to correlate the occurrence of valvular pathologic changes with other features of the disease. He states, for instance, that chorea is much more frequently accompanied by mitral stenosis than is arthritis. In a condition that causes such widespread damage as does rheumatic disease, such correlations are likely to be highly fortuitous even in so large a series as this one. Again, lack of adequate postmortem material might throw some doubt on diagnostic accuracy. The diagnosis of aortic regurgitation based on a diastolic murmur alone, without any of the peripheral vascular phenomena, is a highly hazardous procedure.

The author has little in common with those who admit the occurrence of rheumatic pneumonia. He believes that all the pulmonary findings in connection with rheumatic infection may be satisfactorily explained on some other basis. Nor has he ever seen the Aschoff body or its analogue in the lung. His stand in this matter seems a bit inflexible.

There is an excellent discussion on the "pre-rheumatic state," a term with which the author has little patience. The book is concluded with a sane and conservative discussion of treatment and the necessity for after-care of the child with cardiac disease.

The book constitutes a worth-while addition to the literature on rheumatic infection, but it must not be assumed that all of the opinions expressed will meet with unanimous approval.

Pathologische Physiologie. By Ludolph Krehl. Fourteenth edition. Price, 39.60 marks. Pp. 716. Leipzig: F. C. W. Vogel, 1932.

This massive book, now in its fourteenth edition, is to be the first of a three volume work on the origin, recognition and treatment of disease of the internal organs of the body. The author, who for many years has been the head of the Medical Clinic of Heidelberg, ranks foremost among the older and greater German internists and teachers. His pupils include a number of men who now head other university clinics, such as Stepp in Breslau and Morawitz in Leipzig; his influence on German medicine through his writing and teaching as well as through his prestige and activity in the principal medical societies of Germany is enormous.

The subject matter of the volume at hand is treated from the standpoint of the physician. With all due regard for the importance of investigation on animals, the process of disease in man is considered to be so extraordinarily complex that in the end observations on the patient are of primary importance. Knowledge gained at the bedside thus receives the foremost consideration, although the laboratory is not seriously neglected. There is much that is well known and some material with which the general reader will be less familiar, but the chief value of the work lies in the wealth of problems and questions to stimulate the investigator to further study. There is little didacticism. In fact, the point of view is so philosophic as to make it doubtful whether it will appeal to the "practical" American mind. This is further accentuated by that peculiar verbosity which few German scientific writers seem able to avoid. The book is decidedly not one for the "man who reads and runs;" in fact, the style is so little considerate of the reader's time as to constitute a distinct annoyance. What is said could be compressed at least one-half without the slightest sacrifice of subject matter.

It is impossible in a review to give more than a cursory insight into the mass of material covered. The following topics form the subject matter of the various chapters:

The first section opens with a consideration of constitution in its broadest sense, an obscure subject which is handled in an interesting manner. Infection and immunity are treated somewhat incompletely; at least the more modern conceptions in this field are rather neglected. Fever and metabolism receive adequate consideration with considerable subordination, however, of all but the German literature. It is surprizing that throughout the book one finds scarcely any reference to work in England and America. "Ausländer" discoveries, with few exceptions, are either neglected entirely or considered only through the writings of German reviewers. The section on the nervous system is delightful, particularly in the exposition of such topics as unconsciousness, automatism and the influence of the will. The chapter on the circulation is tiring because of the exhaustive treatment of much obvious material. In the chapters dealing with blood, digestion, respiration and urination, the treatment each subject receives, although frequently confusing, is refreshing and inspiring. The many questions raised about matters which are still unexplained and the doubts expressed regarding much that one is accustomed to accept as fact must prove stimulating to all thoughtful students of medicine.

Hépatites et cirrhoses. Classification, pathogénèse et morphogénèse des hepatites diffuses aiguës, subaiguës et chroniques d'après les notions récentes sur la physio-pathologie hépato-biliare. By Guy Albot, ancien interne des hôpitaux de Paris. Price, 34 francs. Pp. 248, with 56 figures. Paris: Masson & Cie, 1931.

The author of this excellent, well illustrated monograph considers cirrhosis to be the result of various types of hepatitis. The work is primarily anatomic, but the point of view is clinical. The latest histologic methods have been employed in a detailed study of cellular changes noted in the liver under various experimental conditions and also in numerous lesions found at operation or at autopsy in human beings.

Three great groups of diffuse hepatitis are recognized: the toxic-infectious type, the hepatitis of biliary stasis and the hepatitis of venous stasis. The first group, to which the author applies the term "cytolytic hepatitis," includes the familiar clinical syndromes of acute catarrhal jaundice, acute, subacute and chronic atrophy of the liver and atrophic cirrhosis, together with other less common forms, such as the cirrhosis of Hanot. The author distinguishes three stages, demonstrable experimentally and also seen in human material. The initial changes are located in the periportal regions and consist of isolated or grouped mitrochondriolysis and cellular degeneration, accompanied by dilatation of the bile capillaries. In the second stage there is a generalized clarification of all of the cells of the lobule, hypertrophy of the lobule and a proliferation of reticular tissue. The third period is that in which the lesions become asymmetric and are no longer periportal in distribution, but seem to involve the less resistant cells wherever they are located, frequently at the center. If the acute process does not terminate fatally, a cirrhosis develops, the extent of which depends on the severity of the hepatic injury and on its duration. As long as the hepatitis continues, the resulting cirrhosis is progressive.

The group due to biliary stasis may be divided into three varieties: those due to pure stasis, those due to stasis and an accompanying cholangeitis and those due to stasis and accompanied by a diffuse inflammatory process. These changes are well illustrated. In this group the cirrhosis does not progress after the biliary stasis disappears.

The hepatitis and cirrhosis attributed to venous stasis are not considered in detail.

The preface is written by Professor Roussy, who expresses the opinion that the book will take its place in the literature of diseases of the liver. In the opinion of the reviewer, the work is a significant contribution well worth the careful consideration of those interested in hepatic disease.

Cytology and Cellular Pathology of the Nervous System. Edited by Wilder Penfield. Vols. 1, 2 and 3. Price, $30. Pp. 1267. New York: Paul B. Hoeber, Inc., 1932.

The first volume of the system deals with normal and pathologic ganglion cells, nerve fibers, their endings and the nerves of the blood vessels. The second volume treats with mesodermal tissues of the brain, including microglia, meninges, choroid plexus and blood vessels; in another part of this volume are discussed the pineal gland, hypophysis, optic nerve, retina, choroid and papilla. The third volume is largely taken up with tumors, malformations, with which are included tuberous sclerosis, amaurotic family idiocy, Schilder's and Pelizaeus-Merzbacher's diseases and hydrocephalus.

The topics mentioned are only a few of the numerous phases of neuropathology and normal histology of the central and peripheral nervous systems. The most interesting and elaborate contribution is that of del Rio Hortega. It deals with the form of supportive connective brain tissue known as microglia, the cells of which are termed microgliocytes or Hortega cells. These represent the reticuloendothelial system of the central nervous system and are analogous to histiocytes or resting wandering cells of Maximow, also known as polyblasts. They are supposed to perform the function commonly assigned to the neuroglia — to transform damaged brain tissue into lipoids and to remove them to the blood vessels. Equally instructive and exhaustive is the contribution of Boeke on nerve endings, with numerous illustrations. Some of the other contributions are covered in a rather elementary manner, and in some too much space is given to the elaboration of the author's personal views, which in many cases are by no means accepted. The nomenclature is occasionally unusual, is not always sufficiently clear by illustrations and, for these reasons, is somewhat confusing. Because of the great number of contributors some shortcomings, of course, were to be expected in a work dealing with highly specialized topics. The system was evidently prepared

with a view to convey an idea of the fundamentals of the modern normal and pathologic histology of the central and peripheral nervous systems. As an acquaintance with such fundamentals is of utmost importance to the neuropathologist or pathologist in general, as well as to the clinical neurologist, the value of the collective treatise is obvious.

Kolloidreaktionen der Rückenmarkflüssigkeit. Technik, Klinik und Theorie. By Dr. Willy Schmitt. Price, 13.50 marks. Pp. 181. Dresden: Theodore Steinkopff, 1932.

This is a timely book on the subject of colloid reactions of the spinal fluid. It includes theoretical discussions as well as technical and clinical interpretations of data.

The author begins with a discussion of the material used in the colloid test of the spinal fluid, and emphasizes the importance of absolutely clean glassware and the use of standardized substances. There is a detailed technical description of the gold reaction, the Mastix reaction, the parraffin reaction and several other tests. The descriptions are not only set forth in detail, but are compared with the other colloid reactions of the spinal fluid. The author emphasizes the relationship of the individual tests with various pathologic conditions of the brain and spinal cord, and mentions the various colloid reactions obtained by the different methods as applied to disease conditions of these organs. There is also a discussion dealing with those technical methods not used as frequently as the Lange test.

The last chapter deals with the theory underlying the various colloid reactions of the spinal fluid, with particular emphasis on the physicochemical changes that occur. There is also a section of the book devoted to the literature on the various methods described in the text and black and white photographs showing the various reactions in the test tubes with the different methods used.

One does not obtain the impression from reading this book that the various tests employed, excepting the Lange, are of great practical service in the diagnosis of disease conditions. From the academic standpoint, they are of interest and will possibly help the clinician in arriving at an understanding of the pathology of the disease. Each test must be studied separately by the clinician.

For those interested in the subject of colloid reactions of the spinal fluid, this book will be of assistance in many ways.

It is gratifying to note that the type in the book is large and the German is relatively simple, which will aid the English-speaking workers who may have need to refer to the book.

Health Protection for the Preschool Child. By George T. Palmer, Dr. P.N.: Mahew Derryberry and Philip Van Ingen, M.D. Price, $2.50. Pp. 275, with 40 tables and 57 charts. New York: Century Company, 1931.

To have been privileged to hear Dr. Philip Van Ingen and Dr. George T. Palmer recite the contents of this volume at the White House Conference still remains as one of the thrills that great Congress provided. The accuracy, the completeness and the sincerity of purpose of this study were made so impressive through the personality of the speakers that one who heard them almost hesitates to invade the impersonal domain of the printed page. There were many, however, who were not present, and to them will this volume stand as monumental evidence of an untiring effort to obtain facts—facts gleaned from one of the most extensive statistical studies ever attempted.

The pediatric world should be impressed, as a result, with its tremendous strength as a strong contender in the field of preventive medicine, while at the same time it should feel chagrined at the evident failure it has made. We have failed to apply extensively those well founded principles of prevention so efficiently demonstrated when used.

Three specific issues have been investigated, namely: routine health examinations of the preschool child, dental examinations and immunization against

diphtheria and smallpox. In none of these places has the 50 per cent mark been passed in any established normal community, while in many specific instances the percentage is appallingly low.

The urge for a more concerted effort by the pediatrician, the general practitioner and the numerous health departments is so evident through the statistical evidence presented that not to recognize it is nigh on to stupidity.

The members of the committees on medical care for children of the White House Conference deserve the highest praise for this most complete and stimulating study so amply presented in this volume.

Die Zuckerkrankheit und ihre Behandlung im Kindesalter. By Richard Priesel and Richard Wagner, Vienna. Price, 15.60 marks. Pp. 211. Leipzig: Georg Thieme, 1932.

In this small book, which is really a detailed enlargement of the monograph "Die Pathologie und Therapie der kindlichen Zuckerkrankheit," published by the same authors in 1926, Priesel and Wagner have presented an up-to-date discussion of the pathologic physiology, diagnosis and treatment of diabetes in children.

The book is divided into two parts. The first six chapters deal with the theoretical, clinical and laboratory aspects of diabetes, and the last two chapters with treatment. An extensive bibliography, chiefly of European literature, is included. Although the authors have nothing new to present regarding either the clinical or the laboratory phase of diabetes, their large experience and the practical manner in which they present their method of handling children make this a worthwhile volume.

50 Jahre Kongress für innere Medizin, 1882-1932. By Georg Klemperer, Berlin. Paper. Price, 9.80 marks. Pp. 164. Munich: J. F. Bergmann, 1932.

If one desires a brief survey of the trend of medical thought in Central Europe during the last forty or fifty years, this booklet will fill the need fairly well. It consists of a sketch of the advances in the various branches of internal medicine as presented at the meetings of the Congress by its leaders in each subdivision from year to year.

For a source of definite information it cannot be recommended; for a historical outline, it is mildly interesting.

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CONTENTS

PAGE

Urea Clearance Test as an Index of Renal Function. Maurice Bruger, M.D., and Herman O. Mosenthal, M.D., New York:

I. Studies of Normal Subjects 351

II. The Effect of Ingestion of Carbohydrate (Dextrose). 358

Dietary Practices in Relation to the Incidence of Pellagra: I. A Study of Family Dietaries in Leon County, Florida. Margaret R. Sandels, Ph.D., and Eunice Grady, M.S., Tallahassee, Fla. 362

Undulant Fever: An Epidemic of Subclinical Infection with Brucella. Parker Dooley, M.D., Kent, Conn. 373

Low Voltage in the Electrocardiogram: Occurrence and Clinical Significance. Kenneth B. Turner, M.D., New York 380

Treatment of Addison's Disease with Cortin (Hartman): Report of Four Cases. Perry C. Baird, Jr., M.D., and Fuller Albright, M.D., Boston 394

Pericarditis. Harry L. Smith, M.D., and Fredrick A. Willius, M.D., Rochester, Minn.:

IV. Fibrinous Pericarditis and "Soldier's Patches" 410

V. Terminal Pericarditis 415

Sedimentation Rate of Blood Corpuscles in Synovial Fluid and in Plasma: Method of Estimation and Significance in Arthritis. David H. Kling, M.D., New York 419

Clinical Significance of Electrocardiograms with Large Q Waves in Lead III. Thomas Ziskin, M.D., Minneapolis. 435

Production of Nonfatal Vascular Sclerosis in Rabbits by Means of Viosterol (Irradiated Ergosterol). Tom Douglas Spies, M.D., Boston 443

Transient Ventricular Fibrillation: The Clinical and Electrocardiographic Manifestations of the Syncopal Seizures in a Patient with Auriculoventricular Dissociation. Sidney P. Schwartz, M.D., and Abraham Jezer, M.D., New York 450

Localization of Afferent Visceral Impulses in the Spinal Cord. David Davis, M.D.; Emilie U. Goode, A.B., and Soma Weiss, M.D., Boston 470

Diuretic Effects and Changes in Blood and Urinary Metabolites After Digitalis in Normal and in Edematous Persons. A. B. Stockton, M.D., San Francisco 480

Experimental Edema Produced by Plasma Protein Depletion. Michael J. Lepore, M.S., with the Technical Assistance of Augusta B. McCoord, Rochester, N. Y. 488

Book Reviews 506